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General Medicine

Aureomycin in the Treatment of Influenza and Certain Other Acute Respiratory Infections with or Without Pneumonia — FINLAND, MAXWELL, WELLS, E. BUIST, COLLINS, HARVEY S. AND GOCKE, THOMAS M. — *American Journal of Medicine*, 8: 21 (January) 1950.

"Aureomycin was used in the treatment of a miscellaneous group of 41 cases of severe, acute respiratory infections with or without pneumonia."

"The patients were all adults from the medical wards of the Boston City Hospital except for a few who were treated in nearby hospitals or at home. At the time when treatment with aureomycin was started, they were all febrile and acutely ill and either had definite signs and symptoms of pneumonia or they appeared severely ill with acute respiratory symptoms but without definite evidence of pneumonia. . . . The patients have been divided into three groups based on all of the available clinical and laboratory findings.

"Group I includes 18 patients in whom a diagnosis of influenza A was established by serologic test and in a few instances an influenza virus was isolated from pharyngeal washings obtained during the acute phase of the disease and before any aureomycin was given. Most of these patients also had clinical evidence of pulmonary involvement but this was demonstrable by roentgenograms in only 7 of them and in none of the latter was any significant bacterial pathogen identified in cultures of blood or sputum obtained during the acute stage of the disease.

"Group II includes 10 patients who had clinical findings similar to those of group I. Serologic tests in these patients, however, all yielded negative results. In particular, they failed to demonstrate any diagnostic titers or rises in titers of cold agglutinins or influenza antibodies, and the attempts made to isolate influenza viruses from the pharyngeal washings of some of them likewise all failed. Roentgenograms failed to show any pulmonary involvement in any of these 10 patients.

"Group III includes 13 patients all of whom had definite signs of pulmonary consolidation by physical examination and in x-ray films. In all of these patients cultures of blood and sputum failed to yield any significant respiratory pathogens and serologic tests were entirely negative."

There were 20 males and 21 females in this series. Twelve patients were 29 years old or less; 18 were between 30 and 49 years and 11 were 50 years or older.

"Other antimicrobial therapy, either penicillin or sulfadiazine, had been used for from three to seven days in 3 of the patients in group I and in 2 of those in group III. In each of these 5 patients there was no improvement and the fever and symptoms progressed during treatment with these agents."

"Cultures of blood and sputum (or of pharyngeal swabbings when sputum could not be obtained) were made before aureomycin was started and sputum or throat cultures were usually repeated on several occasions during and after treatment. The sputum and pharyngeal cultures were planted routinely in blood broth and on the surface of blood agar plates. Smears of the sputum were examined in Gram-stained preparations and by the Neufeld method."

Serologic studies included tests for cold agglutinins, Streptococcus MG agglutinins, antibodies for influenza A and B and, in a few cases, also complement fixing antibodies for psittacosis and Q fever.

"Almost all of the aureomycin was given by mouth in doses of 1.0 or 0.5 Gm. each at intervals of four or six hours. These doses were reduced or the intervals lengthened in many of the patients after their temperatures reached normal and their

conditions improved. For all of the patients in the three groups the average total dose by mouth was about 12 Gm. given in four days. Some of the patients in group III were treated with larger total doses and over longer periods than those used in the other two groups. Three of the patients in group III also received some parenteral doses to supplement those given by mouth and 1 patient received all of the aureomycin intravenously. The intramuscular doses, which were used in only 2 patients, were given every three or four hours in the form of a glycinate of aureomycin in 100 mg. amounts, each in a volume of 5 cc. of physiologic saline. For each of the intravenous doses either 500 or 250 mg. of aureomycin hydrochloride were given in 1,000 or 1,500 cc. of physiologic saline or dextrose solution and allowed to run in slowly, usually over a period of an hour or more."

The inclusion of patients in group I was based on the demonstration of a diagnostic rise in titer of antibodies for influenza A virus and in 5 of these patients such a virus was also isolated from garglings by inoculation of embryonated hens' eggs. "In 2 patients in whom the initial or only blood was obtained more than seven days after the first symptoms of influenza, the titers of influenza A antibodies were high (1:128 in 1 and 1:512 in the other) and may be considered diagnostic. All other serologic tests were negative in each of these patients. These 18 cases occurred during a period of prevalence of influenza that reached its peak in and around Boston during the second and third weeks of March, 1949."

"At the time when the first dose of aureomycin was given these patients all appeared acutely ill with symptoms and other findings which in most respects resembled those of primary atypical pneumonia. They had the characteristic findings of clinical influenza; namely, chilly sensations, malaise and prostration, generalized muscle aching, soreness of the eyes with conjunctival injection and slight sore throat. In addition, all of these patients also had moderately severe cough which was sometimes productive of small amounts of blood-tinged mucoid sputum and they complained of substernal soreness. In a few the onset was with a severe shaking chill. Some of the patients were slightly to moderately dyspneic and cyanotic."

"Most of the patients were first treated with aureomycin on or before the fourth day of their illness." In 2 patients in whom treatment was started on the eighth and eleventh day, respectively, after the onset of the influenza, there had been a complete remission of symptoms for several days. "Several other patients had also had a brief but only partial remission of symptoms earlier."

"The temperature at the time when the first dose of aureomycin was given ranged from 102° to 105° F., except in 1 patient in whom it was 101° F. The white blood counts were essentially normal except in 3 patients in whom they were slightly elevated and in 1 . . . . in whom it was 19,600."

"The findings in the lungs were consistent with tracheobronchitis or atypical pneumonia." Under the former designation are included those in whom there were diffuse musical rales and, except in 2 patients, there were also numerous crepitant rales, usually limited to one or both lung bases. "Roentgenograms in these cases, however, showed only increased bronchial markings without any areas of increased density in the lung parenchyma. In those listed as atypical pneumonia the physical signs were essentially the same except that crepitant rales were more prominent, there was slight dulness over some part of the lungs and the x-ray films in all these patients showed areas of soft, mottled densities similar to those usually seen in cases of primary atypical pneumonia."

"All of the blood cultures taken in these patients yielded no growth. In those patients who were listed as having atypical pneumonia no significant pathogens were identified in any of the cultures of the sputum or pharyngeal swabs. The growth in these cultures was usually scant and *Streptococcus viridans* and/or *Neisseria catarrhalis* usually predominated." However, among those who showed no intrapulmonary lesions by x-ray and who are listed as having tracheobronchitis, these cultures yielded a predominant growth of hemolytic streptococci in 5 cases and of hemolytic *Staphylococcus aureus* in 2 others.

"The severity of the symptoms was estimated in these patients at the time aureo-

mycin treatment was undertaken. In only 2 of the patients was the illness considered to be mild; in most of the others it was estimated as being of moderate severity and in 4 patients it was considered to be severe."

"The improvement that occurred in the clinical condition of this group of patients following the initiation of aureomycin therapy was quite striking and on the whole was either similar to or even more impressive than that which was observed in patients with pneumococcal or primary atypical pneumonia. There was a major and sustained drop in temperature in every case within the first 36 hours and in all but 2 of the patients this had occurred within 24 hours after the first dose of aureomycin. In only 3 of the patients did the temperature rise to 100° F. on the third day; all of the others were entirely afebrile within 48 hours.

"Improvement in symptoms was equally rapid. All of the major symptoms of acute illness had abated within 24 hours in all but 2 of the patients and the latter improved markedly during the second day and were free of symptoms by the end of the third day. The remaining patients were essentially symptom free by the end of the second day. Cough persisted in 4 patients for periods of 5 to 10 days but this became progressively less distressing and gradually cleared during this time."

One patient had intense headache and signs of meningeal irritation before aureomycin was started. "The cerebrospinal fluid findings at this time were those of a benign lymphocytic meningitis. This patient's fever and symptoms including the headache subsided promptly, as in the other patients, except that nausea and vomiting continued for two days. Attempts were made to isolate a virus from throat washings and spinal fluid. Influenza A virus was isolated from the former but could not be demonstrated in the latter."

"The rales and x-ray shadows in the lungs also cleared quite rapidly. By physical examination the lungs had entirely cleared within five to seven days in every case. X-rays showed clear lung fields in every instance in the films taken between the seventh and the ninth day after aureomycin was started. In most of the patients the lungs were entirely clear before the fifth day."

"In view of the established diagnosis of influenza in the present cases it is obviously not possible unequivocally to relate the observed improvement in these cases to the effects of aureomycin. These cases, however, do not represent 'average' cases of influenza since they were selected for aureomycin therapy only because of the severity of symptoms and because pulmonary complications were already present or suspected. When judged by the marked and rapid improvement that occurred with great regularity and in direct relation to the administration of aureomycin, the beneficial effect of the antibiotic appeared to be quite impressive in all but 3 of these 18 patients and even these 3 patients improved steadily though less rapidly after treatment was started. This improvement may, of course, have been coincidental in some of the patients but that seemed to be very unlikely in most of them."

"The 10 patients included in group II had symptoms resembling those of the patients with influenza in group I. However, there was no roentgenographic evidence of pulmonary involvement in any of these patients and the lungs were clear to physical examination, except for some scattered musical rales heard in 3 of the patients. Furthermore, all of the serologic tests, including those for influenza A and B, gave entirely negative results. Inoculation of throat washings from 5 of these patients into embryonated hens' eggs also failed to yield any viruses. Only 5 of the cases in this group including 1 of those in which virus isolation was attempted occurred during the period when proved influenza A was prevalent.

"Blood cultures in these patients were all negative. Each throat culture from 2 of these patients and cultures of mucopurulent sputum in a third, all obtained before aureomycin was started, yielded a predominant growth of beta hemolytic streptococci. No significant pathogens could be identified in similar cultures from the remaining patients, *Str. viridans* and Neisseria predominating in these cultures. Pharyngitis was more prominent in the 3 patients from whom hemolytic streptococci were cultured than in the others, and in 2 of those 3 patients there was an

exudative tonsillitis and some cervical adenitis. The diagnosis in the remaining patients was 'clinical influenza,' or 'undifferentiated acute respiratory disease' with tracheobronchitis.

"Treatment with aureomycin was started on or before the fourth day of illness in 6 of the patients and on the fifth or sixth day in the others. They were all acutely ill at the time and their temperatures ranged between 102° and 104.6° F. The leukocyte counts were essentially normal in half of the patients and ranged from 16,300 to 21,600 in the others. From the symptoms and general appearance of these patients the severity of their illness was characterized as mild in 3 and as moderate in the others. None of these patients had received any antimicrobial therapy for this illness before aureomycin was started.

"In all these patients the temperature returned to normal between 12 and 24 hours after the first dose of aureomycin except in 2 who had secondary rises in temperature to 99.4° F. during the second day. Symptomatic improvement generally paralleled the drop in the temperature in each instance. In 1 of the patients a coexisting pyuria and *E. coli* bacilluria also cleared completely within two days.

"The rapidity and the regularity with which aureomycin administration was followed by marked improvement in fever and symptoms in these patients strongly suggests that the antibiotic was responsible in some measure for these beneficial effects, or at least for hastening the recovery."

Group III was a heterogeneous group comprising the aureomycin-treated patients with pneumonia which could not be classified etiologically. "Inclusion of the patients in this group is based on the demonstration of definite areas of consolidation in the lungs by both physical examination and x-ray and the failure to identify any likely etiologic agent, either in the cultures of blood and sputum or by any of the serologic tests employed. Furthermore, in none of these patients did the symptoms or pulmonary findings resemble those which are considered to be characteristic of so-called viral pneumonias. Clinically, 5 of these cases were classical cases of 'primary lobar pneumonia' while in each of the remaining 8 the pneumonia occurred either as a complication or as a terminal event in the course of some other major illness and could be characterized in all but 1 instance as atypical or bronchopneumonia. These two subgroups may best be considered separately.

"Patients with 'Primary Lobar Pneumonia.'—In the first 5 patients the symptoms and physical and x-ray signs in the lungs could be considered as characteristic of those found in classical cases of pneumococcal lobar pneumonia but neither pneumococci nor any other significant pathogens could be identified in typical rusty sputum obtained before aureomycin treatment was started. None of these patients had received any previous therapy for this illness.

"Treatment with aureomycin was started in these 5 patients between the first and third day of the disease. The severity of the symptoms at the time varied in the different patients, as did also the fever and leukocyte counts. Four of these patients received aureomycin entirely by mouth, the average dose being 9.5 Gm. in three and one-half days. One patient . . . . was given aureomycin only intravenously, a total of 1.75 Gm. in four doses.

"The response to therapy in these 5 patients was essentially the same as in authentic cases of pneumococcal pneumonia. Fever and symptoms subsided rapidly in 4 of the patients. The fifth patient received only 250 mg. every six hours by mouth during the first day and showed no improvement until the following day after the individual doses were increased to 1.0 Gm. The lungs were entirely clear by the ninth day in 1 of the patients and by the sixth day in the other 4.

"Patients with Pneumonia Complicating Other Conditions.—In the remaining 8 patients the pneumonia may be considered as 'secondary' and the course and response to therapy were necessarily modified, in most of the cases, by the underlying primary disease. In 2 patients the pneumonia began following chest injuries in which fractured ribs were sustained. Aureomycin administration was started on the ninth day in 1 and on the sixth day in the other. The latter was acutely intoxicated at the time and then developed delirium tremens; the former had already received penicillin for seven days without improvement. Both of these patients were febrile

and moderately ill and had high leukocyte counts when aureomycin was started. Doses of 1 Gm. were given every four or six hours. There was a steady drop in temperature in each case; and although there was considerable symptomatic improvement during the first 24 hours, neither of these patients became afebrile or free of symptoms until the end of the third day.

"In 1 patient . . . . the pneumonia occurred during an episode of severe congestive heart failure and aureomycin was started on the fifth day. This patient showed marked improvement during the first 36 hours but complete recovery was delayed because the edema and cardiac symptoms were difficult to control.

"In the remaining 5 patients there was only minor or temporary improvement in the fever and symptoms during aureomycin therapy and in 4 of these patients no additional improvement was observed when penicillin was later given in large doses, in addition. Three of these patients received parenteral as well as oral therapy." Among these 5 patients 3 died of their underlying disease several days after aureomycin was stopped although 1 of them had improved sufficiently to be sent to a nursing home. "The relation of the pneumonia to the underlying disease in the patient with acute rheumatic arthritis was a source of considerable speculation. Neither the pneumonia which was rather mild and not extensive, nor the fever, nor the arthritis appeared to be influenced in the least by the aureomycin. However, in this case only 6 Gm. were given over a period of two days but large doses of penicillin were later given, likewise without effect."

The only untoward effects that were observed from oral aureomycin were some gastrointestinal disturbances of varying severity. "Among the 40 patients included in the present study who received aureomycin hydrochloride by mouth, 20 had some nausea with vomiting but in most of them this was transient and was not severe enough to interfere with continuation of the therapy as planned. In a few, however, it was necessary to reduce the size of individual doses or increase the interval between doses. There were 7 other patients who had only nausea but did not vomit and 4 patients, including 2 of those who had some vomiting, passed bulky, semiformed stools which in only one instance became frequent and watery. There were 11 patients who experienced none of these or any other symptoms from the oral doses.

"The intramuscular doses were all accompanied by pain of varying severity which lasted up to half an hour or longer, and some local tenderness persisted for several hours. Only one of the intravenous injections was followed by a pyrogenic reaction and in a second patient there was a small localized area of cellulitis in the antecubital region where some of the aureomycin solution had extravasated. This cleared in a few days without special treatment. There were no gastrointestinal symptoms from the parenteral injections. In none of the 41 patients was there any fever or rash, or any evidence of toxic effects on the kidney, liver, blood or nervous system that could be ascribed to the aureomycin."

Fatal Agranulocytosis Following Therapy with "Presidon" (3,3-Diethyl-2,4-Dioxotetrahydropyridine). A New Sedative Hypnotic Agent — COVNER, ALBERT H. AND HALPERN, SEYMOUR L. — *New England Journal of Medicine*, 242: 49 (January 12) 1950.

"Among the nonbarbiturate sedative drugs that have recently been introduced has been 3,3-diethyl-2,4-dioxotetrahydropyridine (pyrithyldione), which has been marketed under the trade name of Presidon. The drug was advertised as a sedative hypnotic predictable in its effect, rapid in onset, with negligible side effects, little tendency to habit formation, slight properties of tolerance and completely nontoxic and safe.

"A case of fatal agranulocytosis is presented below, since it is believed that Presidon was the etiologic agent responsible for the patient's fatal illness. It indicates that this sedative hypnotic may not be the safe drug it is believed to be. Since most of the indications for sedatives are elective and the conditions for which it is administered benign, it is best to use drugs that have been shown not to be productive of any serious reactions.

"Case Report.—A 64 year old woman had a 10 year history of multiple com-

plaints and nervous symptoms that were believed to be on the basis of an anxiety state. She had been treated for her symptoms during this long period by numerous sedative and analgesic agents, consisting of various barbiturates—namely, phenobarbital, delvinal sodium, nembutal, seconal and alurate—and the analgesics aspirin and empirin. For the past few years she had been having bowel complaints, and two years previously x-ray films were said to have shown diverticulitis. She stated that she had been failing ever since she had several teeth extracted in January, 1948. In April she began complaining of a dull, aching sensation in the midabdomen associated with a disagreeable sense of nervous anxiety. Between April and December she lost 16 pounds in weight and felt exhausted most of the time. At times the feeling in the abdomen was described as stabbing. It was not relieved by food and alkalies. When the usual sedatives and analgesics failed to give her relief, she was given dilaudid, which proved completely effective. She became addicted to the dilaudid and by November was requiring it every three or four hours. She also complained of poor appetite and constipation without any associated diarrhea. A severe insomnia developed because of nervousness and because of a dry cough that began during the night. To help relieve the insomnia and perhaps to decrease the amount of dilaudid utilized, she was given a trial with Presidon. During the period from November 13 through November 17, she received a total dose of Presidon of nine tablets (equal to 1.8 Gm.). She received the last dose on the night of November 17. This consisted of two tablets (0.4 Gm.) of the drug. She was admitted to the hospital on November 18, under the care of a surgeon, to evaluate her symptoms and to rule out cancer.

"The past history revealed that an appendectomy had been performed several years previously. The rest of the past and family history was irrelevant.

"Physical examination revealed a well developed, underweight, apprehensive woman. Her skin was pale. The heart revealed a soft systolic apical murmur. Abdominal examination was negative except for very slight tenderness on deep pressure just above the umbilicus. The remainder of the physical examination was negative.

"Examination of the blood on November 19 showed a red cell count of 5,180,000, with a hemoglobin of 97 per cent, and a white cell count of 6,000, with 57 per cent neutrophils and 43 per cent lymphocytes; the red blood cells were normal on smear. Urinalysis was negative. The blood sugar and nonprotein nitrogen were normal. The blood sedimentation rate was 3 mm. in one hour. Gastric analysis showed free hydrochloric acid. No abnormalities were seen on sigmoidoscopic examination. X-ray study of the chest demonstrated a minimal atelectasis of the left lower lung not noted on a negative chest x-ray examination two months previously. X-ray studies were otherwise not remarkable.

"The patient was extremely nervous and insisted upon receiving dilaudid every four hours as she was used to doing at home. The basal metabolic rate on November 24 was + 20 to + 25 per cent. The patient continued to be very nervous and on November 25 she was given Lugol's solution, 10 minims three times a day, and 4 mg. (1/16 grain) of phenobarbital three times a day, in addition to the dilaudid. No other antithyroid drugs were administered at any time. On the same day she complained of unusual restlessness, and there was a slight rise of temperature, pulse and respiration. On November 27 she complained of sore throat and headache, severe restlessness and malaise, and at times was incoherent. The situation persisted on the tenth hospital day. On the night of the twelfth hospital day, the temperature rose to 102.4° F., and she complained of rectal pain. On the following day the temperature rose to 103.4° F. Physical examination revealed an acutely ill woman; there was an ulceration in the left tonsillar fossa, and the gums were friable. The rectal area was found to be reddened and firm, with the appearance of a severe cellulitis. Urinalysis was negative. Examination of the blood on that day showed a red cell count of 4,560,000, with a hemoglobin of 88 per cent and a white cell count of 1,600, with 0 neutrophils and 100 per cent lymphocytes. The red cells and platelets were normal on smear.

"The diagnosis of agranulocytosis having been established, the patient was given vigorous treatment during the next six days. She received 100,000 units of penicillin every four hours. In addition, she received during this period streptomycin, 1 Gm. per day, two blood transfusions, crude liver extract (3 cc. intramuscularly daily) and daily administration of Pentnucleotide, pyridoxine hydrochloride, beroccac and parenteral infusions. However, her course was steadily downhill. The temperature varied from 101 to 105.6° F. The pulse was over 100, and the respirations became very rapid, going to 30 and to as high as 60 per minute. On December 3 the white cell count was 1,150, with 100 per cent lymphocytes, and the red cell count 4,030,000, with a hemoglobin of 88 per cent; a blood smear was normal for red blood cells and platelets. The area around the rectum and vagina had become gangrenous, but no pus was apparent. Culture from the perineal region showed *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*). Blood culture was negative. Bone marrow examination revealed the complete absence of developing and mature polymorphonuclear leukocytes. There was some generalized hypoplasia, with a decrease in nucleated red blood cells. Megakaryocytes were present in normal numbers. On December 4 a smear showed 1 per cent myelocytes, 12 per cent monocytes and 87 per cent lymphocytes. On December 5 the patient appeared worse and lapsed into coma. Her pulse was weak, thready and rapid. She was digitalized with cedilanid, and the other leukopoietic and antibiotic drugs were continued. A blood culture revealed the presence of *Ps. aeruginosa*. On December 6 the white cell count was reported at 3,400, with 3 per cent stab cells, 4 per cent monocytes and 93 per cent lymphocytes. She remained comatose and died that evening (the eighteenth hospital day) 19 days after the last dose of Presidon and 12 days after the onset of symptoms.

"Autopsy revealed the bone marrow to be slightly more cellular than normal, but with an almost complete absence of cells of the granulocyte series, especially of the more mature forms. There was a necrotizing and phlegmonous proctitis and vulvitis with extension into the perineum and adjacent tissues, and edema and probable phlebothrombosis of the lower extremity. Also, there was acute toxic hyperplasia of the spleen and cloudy swelling and toxic degeneration of the liver and kidney. The other findings included slight cardiac dilatation, with acute toxic myocardosis, acute visceral congestion, slight hyperplasia of the thyroid gland, tubular degeneration of the adrenal cortex, slight arteriosclerosis of the aorta and marked hypertrophic arthritis involving especially the vertebral bodies and hands. (The head was not examined.)"

"The possibility that the agranulocytosis is due to another drug has to be excluded. . . . The only drugs taken by the patient described above in the few weeks prior to hospital admission were dilaudid, phenobarbital and Presidon. Dilaudid and the other opiates have never been implicated in agranulocytosis. The barbiturates have been suspected on several occasions, but rarely has there been clearcut proof of their relation to the disease. In most cases the involved barbiturate was taken in the form of a compound that contained also aminopyrine." Most authors believe that the barbiturates apparently do not cause agranulocytosis, and the present authors are impelled to conclude that they were blameless in the case reported above. "In the several months prior to the fatal illness, no other medication but dilaudid and some barbiturates were taken by the patient, and there was no evidence of any specific infection or of exposure to toxic chemicals. In the two weeks before admission only dilaudid and Presidon were administered. Since dilaudid and the barbiturates are clearly ruled out, Presidon remains as the almost certain cause of the agranulocytosis."

The time relation for the development of the agranulocytosis is also correct, for it has been shown that two weeks may be required for the maturation of the myeloblast to the mature five-lobed polymorphonuclear neutrophilic leukocyte. "It is possible that the superimposed infection aggravated the toxic depression of the bone marrow in the case reported above. It is interesting to note the monocytic response in the last two days. This has been heralded as a good prognostic sign. Had the patient been able to survive the over-

whelming septicemia and toxicity, she might very well have recovered."

"Failures in therapy still occur for several reasons. Poor results are to be expected if the damage to the bone marrow is massive enough for myelopoiesis to be more than transiently impeded or destroyed. The nature of secondary invaders, the age of the patient, previous state of health and ability to combat bacterial invaders when the patient is stripped of his granulocytic defense are all involved."

"After this article had been submitted for publication, word was received from the manufacturers of Presidon announcing the recall of supplies of the drug because of reports made to them of leukopenia and agranulocytosis occurring in patients who had been using Presidon." The authors believe, however, that this case should be recorded in the literature because of the important warnings and conclusions that may be drawn from it.

Remote Effects of Hypertension in Pregnancy — BENSON, RALPH C. — *Northwest Medicine*, 49: 29 (January) 1950.

Toxemia of pregnancy is a symptom complex characterized by hypertension, albuminuria and edema, and is generally associated with vascular, gastrointestinal and occasionally neurologic symptoms. "Hypertension is merely a sign of disease but it is a prominent feature of the toxemias complicating pregnancy."

"Preeclampsia usually develops with a rather sudden elevation of the blood pressure, increasing amounts of albumin in the urine and symptoms such as headache, scotomas, nausea and vomiting. Four per cent of patients with preeclampsia develop the added sign of convulsions and are then considered eclamptics. Preeclampsia and eclampsia are seen after the twenty-eighth week of gestation as contrasted with those other toxemic patients, in whom hypertension is noted before the seventh month of pregnancy."

"It is no longer accepted that uncomplicated pregnancy will lessen hypertension. On the contrary, more than 30 per cent of these hypertensive women will, in all probability, develop superimposed severe preeclampsia and about 30 per cent of the so-called mild preeclampsias will go on to severe preeclampsia. In addition, some 30 per cent of the entire group of the toxemias of pregnancy will be found to have developed a hypertension of more or less fixed type six months after delivery and this hypertension will be aggravated, in all likelihood, by later pregnancies. In these women, therefore, the need for contraception is all the more definite."

The reduction of maternal and fetal mortality, of course, is the goal. The writer has a saying in his clinic that, "If a patient has even one eclamptic convulsion, her chance of dying in childbirth is multiplied seven times!" "These patients die in a variety of ways. They may develop sudden irreversible uremia; they may die in coma, in pulmonary edema, from cardiac failure or from a cerebrovascular accident. They may aspirate vomitus during the course of their tonic and clonic convulsions."

One writer found that the total infant mortality rose from 6.8 to 21 per cent after convulsions. "The infants usually die of hypoxia and/or acidosis during the course of the tetanic uterine contraction which usually accompanies the general tonic and clonic convulsions." Therefore, one must be alert to prevent hypertension and to minimize its secondary complications. The immediate aim of the obstetrician and the internist-consultant should be the successful treatment of the toxemia. To prevent convulsions one is forced to employ symptomatic therapy. The writer prescribes magnesium sulfate intravenously or intramuscularly, together with other sedatives. "These agents tend to reduce nervous irritability and encourage a lowered blood pressure." The writer administers aqueous hypertonic glucose intravenously and serum albumin to increase the urinary output and to mobilize excessive tissue fluids. He seeks to deliver the patient without harm or handicap so far as future pregnancies are concerned.

"Obstetricians are under pressure to do more cesarean sections in the prodromal stage of the toxemias of pregnancy after palliation on the assumption that surgery avoids difficulty in the postdromal phase of the toxemia." If a patient does not respond to intensive therapy over a reason-

able period of time, the writer does believe that cesarean section should be considered. "However, a cesarean section is not a simple solution to the problem. Pelvic and wound infections occur; some patients die under anesthesia; others require subsequent surgery and repeat cesarean sections because of a faulty uterine scar." If one can reasonably expect the prompt delivery of a healthy baby, the writer prefers to deliver the patient per vaginam.

When does one deliver the patient? If the multigravida is in her eighth lunar month of pregnancy and develops severe preeclampsia, perhaps superimposed upon a hypertensive disease, should one quickly rupture the membranes and deliver the woman to avoid immediate and late complications of hypertension? With such an attitude one would probably deliver many nonviable children. If one could treat the patient medically for a while, a few weeks perhaps, and then induce labor, the infant might probably survive vaginal delivery. One sometimes pays a high premium in maternal vascular damage for the waiting period. "This is the crux of the philosophy of palliation in the preeclamptic toxemias."

"If a patient with a progressive, severe hypertension is seen in the first trimester of pregnancy, therapeutic abortion is probably justified. If interruption of pregnancy is not accomplished, such a hypertensive patient will very often slip into a critical condition and the infant will be lost by fetal death in utero, following placental infarction."

"The sedation and pressor tests, eyeground appraisal, urine concentration tests, urine sedimentation counts, special kidney clearance procedures will all aid in an evaluation of the patient's risk. Roentgenograms to determine the size of the heart and electrocardiography have helped greatly in the medical management of patients with hypertensive disease as well as those with the other toxemias of pregnancy. A favorable response to digitalization in a critical toxemia patient may make a satisfactory termination of pregnancy possible.

"It is now suggested that eclampsia may imply a special type of encephalopathy, in which hypertension and edema are synergistic causative factors." Possibly, if one takes electroencephalograms before delivery, particularly in the patient with a toxemia, one will become more cognizant of such an aberration and will be able to institute early and more intensive anticonvulsant therapy.

The Shoe-Fitting Fluoroscope as a Radiation Hazard — LEWIS, LEON AND CAPLAN, PAUL E. — *California Medicine*, 72: 26 (January) 1950.

This study was directed principally toward an accurate determination of the intensity and relative radiation dosage to which both employees and customers were exposed in the course of normal operations of the shoe-fitting machine. "Even this purpose was not entirely achieved, since it was impossible to maintain sufficient supervision of the shoe salesmen to determine accurately the degree of exposure without producing a nullifying antagonism on their part.

"Instrumentation.—Portable apparatus currently available for the determination of x-ray exposures consists principally of the following: (1) ionization chambers of the pencil dosimeter (minometer or electroscope) type; (2) the ion chamber or ionization rate meters; (3) the dosimeter r-meter; (4) the film badge; (5) the Geiger-Müller counter. Although other investigators have used the dosimeter r-meter for detecting stray radiation, it was considered advisable to use the minometer ionization chambers (Victoreen) for this purpose during the brief periods of operation of the machines. The minometer chambers used have maximum capacities of 10, 100 and 200 mr. Three readings were made at each site in most instances. Excellent reproducibility of results was found and all ionization chamber instruments functioned well under conditions of normal humidity. On foggy and humid days it was impossible to charge the chambers. Victoreen dosimeter r-meter chambers with a capacity of 100 r maximum were used for detecting direct beam radiation.

"For measurement of weekly exposure each salesman was provided with two film badges. One of these was to be worn in the trouser watch pocket and the other in a trouser cuff. Salesladies were requested to place one badge in their clothing near the belt and the other inside a shoe. These

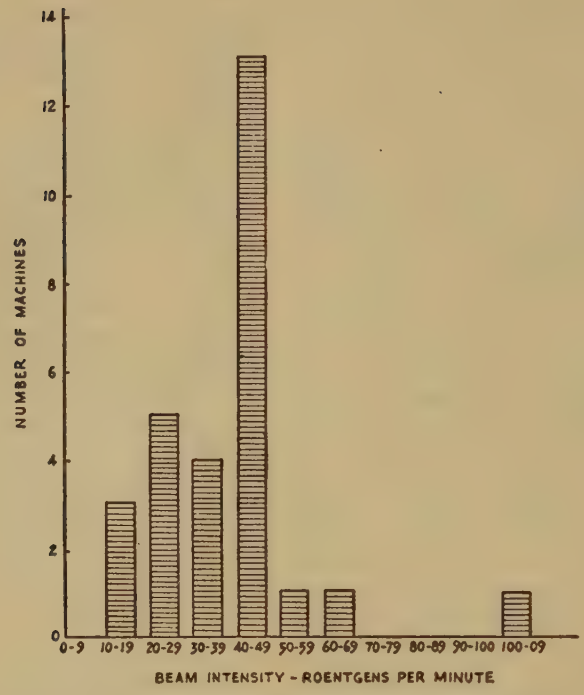

Chart 1.—Distribution of beam intensities in roentgens per minute, measured by placing dosimeter r-meter within shoe-fitting chamber (28 machines).

were worn for 40 hours weekly and exposure was determined by densitometer readings according to standard technique.

"Primary X-Ray Beam Intensity. — Measurements were made directly within the shoe-fitting chamber on 28 machines and by use of the dosimeter r-meter (Victoreen). Exposures were timed for 30 seconds. Table 1 indicates the primary beam dosage of the machines tested. Chart 1 shows the distribution of doses and demonstrates graphically the variation from machine to machine. It will be noted that there was a range from 12 to 107 r per minute, with an average of 38.4 r per minute. Although no tests were made with a customer's foot in the apparatus, these values give a conservative approximation of the range of radiation to which skin and tissue may be subjected. It is of interest here to point out that several shoe salesmen volunteered the information that they frequently placed their hands within the fitting opening to demonstrate to parents and customers the nature of the fit or to place the foot in a more favorable position for viewing while another salesman operated the machine. It would be interesting to determine the actual exposure per customer and the amount of time during which shoe salesmen are subjected to stray radiation during the course of the day. In this study no such measurements were possible except for casual observa-

Table 1.—Direct Beam Exposure to Foot*
Roentgens per Minute

Mean	Median	Maximum	Minimum
38.4	40	107	12

* Measured with Victoreen dosimeter r-meter within foot opening.

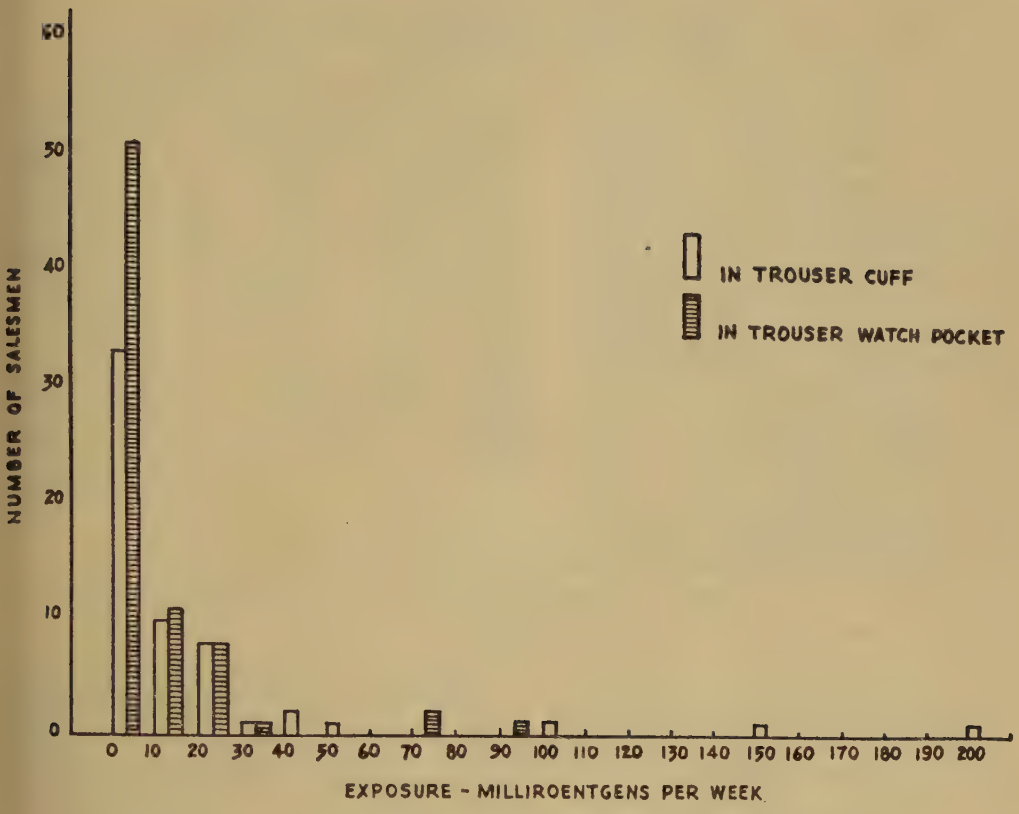

Chart 2.—Range of weekly exposures of shoe salesmen, measured by film badge technique.

tions which indicated that there was little inclination to be satisfied with a single-timed exposure. Some of the machines were set for 5 seconds and others for 20 to 30 seconds, but these times were frequently found to be insufficient for customer satisfaction. The possibilities for multiple exposure to the direct beam are obvious when one considers the frequency with which some patrons may go from store to store, at each of which there may be several fittings.

"Seventy-seven salesmen cooperated in this part of the study and readings were made of film badges which were worn for one week in each instance. There were several instances in which the film badges were lost or misplaced and these, unfortunately, were usually the film badges placed in the trouser cuffs. Table 2 and chart 2

Table 2.—Stray Radiation Exposure to Salesmen*

Location	No. of Salesmen	Exposure-mr per week: Mean	100 to 300	10 to 100	Not Detectable
In trouser cuff	58	15.0	2	23	33
In watch pocket	74	7.1	0	22	52

* Measured by film badge densitometer technique.

Table 3.—Stray Radiation Around Machine*

Position (See chart 3)	Total No. Readings Made	Exposure-mr per Minute of Operation: Mean	100-400	10-100	1-10	Not Detectable
1. Eyepieces	24	1.0	0	0	4	20
2. Floor—left side	38	4.1	0	6	6	26
3. Floor—right side	37	1.4	0	1	8	28
4. Floor—front	37	1.9	0	3	8	26
5. Operator's switch	22	3.7	0	4	2	16
6. Beside foot	18	100.0	10	8	0	0
7. At opening	32	247.8	32+	0	0	0
8. 1 ft. from opening	22	60.2	4	18	0	0
9. 2 ft. from opening	22	22.5	0	20	2	0
10. 3 ft. from opening	11	23.4	1	7	3	0
6 ft. from opening	11	3.5	0	1	3	7

* Measured with minometer ionization chamber pencils.

\+ Readings of 400 mr or above on seven machines.

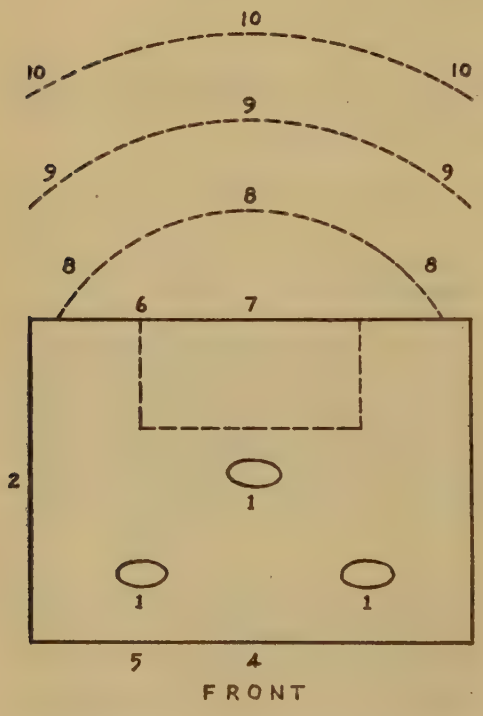

Chart 3.—Plan view of shoe-fitting machine. Numbers refer to points at which stray radiation was measured (see table 3).

indicate the range of dosage in the two parts of the body surveyed. These data are admittedly rough since there were several instances in which it was known that film badges originally placed in the trouser cuff were later placed in the watch pocket and occasionally there were days during which the film badges were not worn at all. This may account for the relatively large number of zero readings reported.

"Stray Radiation.—Chart 3 represents a plan view of a shoe-fitting machine. Points at which measurements were made are indicated by numbers 1 to 10. The extent of leakage of radiation about the machine is shown in table 3 for the various positions tested. These observations were made with Victoreen minometer ionization chambers with capacities of 10, 100 and 200 mr. It will be noted that a high degree of scatter was found at the foot opening of the machine and that fairly high values also were obtained when the instrument was placed beside the foot being examined. Although the leaded glass shield usually protected the eyes, there were some instances in which as much as 9 mr per minute was recorded at the viewing point. This was probably attributable to the fact that the leaded glass was not always placed in proper position and leakage occurred around the margin."

"Sufficient information has now been accumulated to prove that the fluoroscopic shoe-fitting machine represents a potential, if not obvious, hazard. The question which

must be answered by health authorities is whether these machines should be subjected to strict regulation or eliminated entirely. The answer to this question depends in part upon a consideration of the usefulness of the devices. If fluoroscopy is essential to shoe fitting, its use can probably be rendered safe. This will necessarily involve training of personnel and frequent inspection, the efficacy of which is always limited. In this connection it is interesting that of the 77 salesmen interviewed at least half were of the opinion that the machine was not of use in scientific shoe fitting. Most of them were of the opinion that it was chiefly useful for sales promotion and only a small minority favored its use for more satisfactory fitting, particularly of children."

Bilateral Cortical Necrosis of the Kidneys — WERNER, WILLIAM A., MUCKERMAN, RICHARD I. C. AND ALLEN, HOLLIS N. — *Journal of Missouri State Medical Association*, 47: 20 (January) 1950.

"Bilateral renal cortical necrosis is an entity characterized by a patchy or complete necrosis of the cortical substance of both kidneys."

"Following are 2 cases of bilateral renal cortical necrosis encountered in St. John's Hospital."

"Case 1.—A 26 year old housewife was admitted on December 7, 1946. She had developed a respiratory infection two days prior to entry and had become severely dyspneic. The past history was normal except for hay fever. Regional and family histories contained nothing unusual.

"Significant physical findings consisted of temperature 101.4° F., blood pressure 114/85 and impaired resonance with rales scattered over both lung fields. The admission diagnosis was virus pneumonia.

"The initial blood count showed 9,200 white blood cells with slight increase in the segmented forms. Subsequently she developed a leukocytosis.

"Sulfadiazine was begun on admission and stopped on the second day when it was apparent that the patient was becoming anuric. She became worse gradually. On December 11, 1946, the kidney pelves were washed out in an attempt to remove any mechanical blockage. Urethral catheters were left in place. She became comatose on the following day. She continued to grow worse, remaining anuric, and died in uremia on December 15, 1946. Autopsy revealed the typical lesions of bilateral renal cortical necrosis.

"Case 2.—A 29 year old housewife, multipara, was admitted to another hospital on September 12, 1948, and delivered a living male child on September 19 after several attempts at induction of labor. On the tenth postpartum day she developed a chill with a temperature of 103 F. but had no specific complaints. Physical examination and urinalysis were normal. Penicillin was started. Two hours after the first dose of sulfadiazine, her temperature went to 106 F. and no further sulfadiazine was given at that time. Blood counts showed a moderate leukocytosis and a slight anemia.

"A blood transfusion was started and after 100 cc. the patient developed a severe chill, and soon went into shock. Shortly thereafter an additional 200 cc. of the same blood was given before it was discovered that the blood was a type A and the patient was type O. Shock was combated successfully and the patient's temperature returned to normal.

"On the twelfth postpartum day she became anuric. Ureteral catheterization yielded no urine in six hours. A right renal decapsulation was done and the kidney was blue-black in color with the capsule under no tension and tissue apparently in a good state of hydration. Postoperatively, she received only enough parenteral fluids to cover the calculated loss and to maintain blood chlorides. She was transferred to St. John's Hospital for peritoneal lavage but died shortly after admission.

"The significant autopsy finding was a bilateral renal cortical necrosis."

Two additional cases are reported, 1 of which was eclampsia, to emphasize the clinical similarity of bilateral renal cortical necrosis, lower nephron nephrosis and certain cases of eclampsia.

"Case 3.—A 31 year old housewife had been delivered of a full term stillborn infant four days prior to admission to the hospital. The placenta had been extracted manually and eversion of the uterus fol-

lowed. She was erroneously thought to be Rh positive and was given a transfusion. A severe reaction followed. A subsequent Rh determination revealed her to be negative. Anuria developed after delivery.

"She was treated supportively with parenteral fluids until her nonprotein nitrogen reached 108 mg. per cent. Her prognosis was thought to be poor and she was referred to St. John's Hospital for peritoneal lavage.

"Her past history was noncontributory except for childbirth and the removal of an ovarian cyst nine years prior to the present illness.

"Physical examination revealed a well developed, well nourished woman who was edematous about the face. The blood pressure was 120/60. The remainder of the examination was normal except for a uterus consistent with the fourth postpartum day.

"Continuous transperitoneal lavage with 2.5 per cent glucose in Hartmann's solution with heparin was carried out and penicillin was begun on the day of admission and continued for five days.

"Laboratory examinations on admission showed red blood cells, 2,990,000; Hg. 7.7 Gm.; white blood cells 11,200, stabs 5, segments 73, lymphocytes 18, monocytes 4. Subsequent counts revealed essentially the same picture except for a rise of the red count to 3,560,000.

"During her hospital stay all urine examinations revealed many red and white cells and varying amounts of albumin.

"The nonprotein nitrogen was 100 mg. per cent on admission and it did not fall appreciably until 16 days after admission to St. John's Hospital when it fell to 75 mg. per cent. Within two days it had fallen to 40 mg. per cent.

"Blood chlorides were kept at low normal levels.

"The peritoneal lavage fluid contained large quantities of nonprotein nitrogen, although no accurate quantitative studies were done.

"The urine output per 24 hours gradually increased from 75 cc. the day following admission to 400 cc. on the eighth day following admission. The output suddenly jumped to 1,075 cc. on the ninth day.

"The patient was discharged clinically well on the twenty-second day after admission.

"Case 4.—A primipara entered in labor on May 24, 1947. On the basis of slight albuminuria and an elevated blood pressure of 150/110, a diagnosis of preeclampsia had been made. After 7 hours and 20 minutes of labor, a breech, double footling stillborn infant was delivered at 9:35 A.M.

"The patient bled excessively following the delivery. Uterine packing failed to control the bleeding. By evening 6,000 cc. of blood and plasma had been given. An attempt was made to ligate the uterine arteries from below but bleeding continued. The patient had been anuric all day.

"At 7:25 P.M. a supracervical hysterectomy was done.

"Large quantities of blood, plasma and glucose were given throughout the following day. Her urinary output was 50 cc.

"The patient lapsed into shock on May 26, 1947, and died. The autopsy revealed the kidney and liver consistent with eclampsia. The microscopic sections of the liver show extensive areas of necrosis, the necrotic areas occupying apparently 75 to 80 per cent of the total liver substance. Small islands of moderately normal liver tissue are seen about many of the periportal spaces and toward the edge of the liver.

"Microscopic section of the kidney shows a variety of pathologic conditions. The glomeruli are cellular, giving the typical microscopic picture of acute glomerular nephritis. Many of the glomeruli are completely devoid of blood and other glomeruli are completely filled with blood, giving the appearance of early necrosis or at least thrombosis in the glomeruli. The capsules of the glomeruli are thickened somewhat. The proximal convoluted tubules show wide areas of almost complete destruction. In places the convoluted tubules appear as broad columns of eosinophilic material, in areas showing no nuclei, or, at the best, eosinophilic shadows of former nuclei. In some areas the destruction is not as complete but in these areas there is a cloudy swelling with destruction of large amounts of the proximal tubular cells. In the outer part of the cortex, the distal tubules are not unusual but lower down toward the collecting tubules,

many of them are filled with what is apparently blood or at least an eosinophilic debris. There is edema in the collecting tubules and in areas there are broad sinuses filled with blood and apparent hemorrhage between the tubules. In some areas in the outer cortex, there are small fields of apparently complete necrosis. The blood vessels show a necrotic wall and in these areas there is a moderate infiltration of neutrophils. The general appearance is that of acute glomeral nephritis with lower nephron nephrosis, apparently going on to the degree of partial cortical necrosis."

"From the cases presented, it becomes evident that the clinical picture alone may provide little basis for the differentiation of bilateral renal cortical necrosis, post-transfusion uremia (lower nephron nephrosis) and certain instances of eclampsia. Antecedent factors such as shock, incompatible transfusion and sulfonamides may or may not offer a reliable diagnostic guide."

Whatever is shown to be the eventual relationship of these three entities, the writers believe that eclampsia and bilateral renal cortical necrosis should be considered along with lower nephron nephrosis in the differential diagnosis of postpartum renal shutdown.

The Immediate and Remote Results of Streptomycin Treatment of Pharyngolaryngeal Tuberculosis — MEDA, PIERO AND GIORGI, PAOLO — *L'Ospedale Maggiore*, 37: 419 (November) 1949.

Laryngeal and pharyngeal tuberculosis is better and more rapidly influenced by streptomycin treatment than pulmonary tuberculosis. Combinations with vitamin A, sulfones, and paraamino salicylic acid are used. Local streptomycin treatment has been used in the form of ordinary inhalation and spray atomization as aerosol, usually in daily doses of 0.1 to 0.5 Gm. in one or more applications; these local applications control the dysphagia and also have a direct effect on the anatomical lesion, but this effect is definitely inferior to that of systemic treatment. Local applications are not free of an irritating effect. While the pharyngeal lesions heal constantly the laryngeal ones sometimes are only improved or remain unchanged. The more recent lesions always give better results, and the pharyngeal lesions are usually more recent and of a more rapid course than the laryngeal ones. The miliary forms respond best to streptomycin treatment, then follow the infiltrative and edematous, and then the ulcerovegetating forms, which are always of longer standing. Functional and anatomical effects must be distinguished. Painful dysphagia and dysphonia are influenced in practically all cases; the dysphagia may improve within a few days and completely subside within 10 to 15 days, while the dysphonia is more intensely linked to anatomical alterations and responds more slowly and less evidently. The anatomical effects are less constant and slower to appear but are almost always present.

The course differs from that of spontaneous cure or cure by other treatments. The associated suppurative phenomena disappear, the underlying tuberculous infiltrations become clean, and reduced in size, and finally disappear, the mucosa appears smooth and clean, and the specific lesions seem to retract as if drying out. Complete restoration of normal conditions may result but more frequently cicatricial formations result, sometimes with deformations, amputations and stenoses. Superficial processes may lead to complete anatomical restoration while sclerotic deforming processes result in the deeper layers. The pharyngolaryngeal lesions respond better in individuals with recent pulmonary lesions which themselves respond well, although always more slowly than the laryngeal ones.

Over a period of slightly more than a year the authors observed 37 cases of purely laryngeal, 5 of pharyngolaryngeal, and 1 of purely pharyngeal tuberculosis. All patients received streptomycin in moderate doses because of scarcity of the material. The daily doses ranged between 0.5 and 2.0 Gm. and the total dosage between 20 and 90 Gm. There were 30 cures, and 9 cases of improvement while 4 patients were not influenced. The corresponding figures were 21, 6 and 3 for patients with chronic, and 9, 3 and 1 for patients with acute or subacute pulmonary lesions; the figures were 10, 4 and 1 for old, and 20, 5 and 3 for recent local lesions. Complete

anatomical restoration was found in 23, and scars in 7 cases, 5 of which involved patients with acute or subacute pulmonary lesions; 2 patients developed deformations and respiratory distress, and in 1 of them tracheotomy was required. Cicatricial lesions of the epiglottis or the true and false vocal cords had scanty influence on voice and respiration while those involving the joints or the perichondrium led to functional disturbances.

Local treatment was used only in a few of these cases and did not seem to modify the results. Dysphagia subsided within one to two weeks, while dysphonia responded more slowly and with a greater parallelism to the anatomical modifications. The infiltrations responded after one to several months. The general condition improved in all cases, due to a true systemic effect of detoxification. The daily or total dosage did not seem to have a determining effect in this respect, and equally good results were obtained in some cases with low as in others with higher doses. Toxic disturbances were rare and slight, limited to some vertigo and tinnitus. The frequency of pharyngolaryngeal tuberculous manifestations seems to decrease with streptomycin treatment of pulmonary tuberculosis. Three of the authors' patients succumbed to pulmonary tuberculosis while the laryngeal manifestations remained cured. The sputum remains positive in many cases after cure of the laryngeal manifestations, indicating a dissociation of the effect of the antibiotic with respect to larynx and lungs. This dissociation must be linked to differences in structure and vascularization of the lesions in different localizations; in the lungs caseation or fibrosis and reduced vascularization may account for a decreased supply of the antibiotic and for resulting decreased efficacy. With respect to caseation, the hypothesis of chemical combinations with streptomycin, annulling its efficacy, seems rather likely, and acute pulmonary lesions comparable to the pharyngolaryngeal ones, with absence of fibrosis and caseation, and with infiltration of a more or less edematous or ulcerous type with rich vascularization respond best to antibiotic treatment.

The incidence of cure of laryngeal tuberculosis was higher in the cases with chronic pulmonary lesions than in those with acute pulmonary lesions, but recent laryngeal manifestations responded better than older ones. Ulcerative processes are more often the expression of acute processes and therefore respond better than simple infiltrative ones. Pharyngeal lesions usually appeared secondarily to laryngeal ones, both in cases with chronic and with acute pulmonary lesions, but showed better healing in the former.

A miliary type of pharyngeal tuberculosis developed in 2 cases of laryngeal tuberculosis during streptomycin treatment, at a time when the laryngeal lesions showed regression, but its aspect and course definitely showed the effect of the streptomycin treatment. Even vast perichondritic infiltrations may rapidly heal with perfect anatomical restoration but in some cases deformations and stenosis will result. With streptomycin treatment, tracheotomy is feasible without the otherwise attending risk of reacutization or diffusion of the tuberculous process.

One Year of Streptomycin Treatment of Tuberculosis. Observations and Results — MARCORA, FERRUCCIO — *L'Ospedale Maggiore*, 37: 377 (November) 1949.

There is still no consensus of opinion concerning the mode of use of streptomycin in tuberculosis, the optimal dosage, and the duration of clinical cures, particularly in certain forms like tuberculous meningitis. At first in the author's hospital streptomycin treatment was limited to miliary, meningeal, laryngeal and renal tuberculosis, but later galloping types of pulmonary tuberculosis were also treated. The patients could not be selected according to rigorous criteria as frequently miliary and meningeal tuberculosis supervene in patients with chronic tuberculous affections, and as on the other hand, the acute types may later lead to secondary specific lesions not belonging to the types selected for treatment. The author's material is divided into miliary tuberculosis, solitary or isolated meningeal tuberculosis in which neither clinically nor roentgenologically, a tuberculous focus as presumptive point of origin of the meningeal localization can be demonstrated, associated miliary and meningeal tuberculosis, laryn-

geal tuberculosis, always concomitant to more or less severe manifestations of pulmonary tuberculosis, and finally various forms of tuberculosis.

It has been pointed out that optimal results can be obtained with small doses of streptomycin and that the high dosage formerly recommended should not be used because of the frequency of toxic manifestations and of inhibition of indispensable reparatory processes. Therefore, the streptomycin was given in an average dose of 0.01 Gm. per Kg. body weight daily, and generally the dose of 0.6 Gm. was not exceeded, given in doses of 0.15 Gm. at intervals of six hours. In tuberculous meningitis 0.55 Gm. were given intramuscularly and 0.05 Gm. intraspinally. Only in laryngeal tuberculosis a dose of 1.0 Gm. was used, half of it intramuscularly and half by inhalation. When ordinary spinal puncture revealed a low block, suboccipital puncture was used without inconveniences. Over a period of a year a total of 2,531 lumbar and 907 suboccipital injections was carried out. The hospital stay varied from four days to a year. The highest total amount of streptomycin given to 1 patient was 264.2 Gm. Additional treatment included intravenous sulfone infections at intervals of two days in all cases, and intramuscular injections of large doses of vitamins A and D.

In some cases, transfusions, injections of tubercle bacillus lysates, pneumothorax treatment, and paraamino salicylic acid was used, the latter either combined with streptomycin, or in cases with phenomena of intolerance and patients who had left the hospital instead of streptomycin. Opportune hormonal treatment was instituted in cases with signs of dysendocrinia. The course of each case was studied carefully both clinically and with laboratory methods; in all cases of tuberculous meningitis the spinal fluid was examined daily with all laboratory methods, and eyegrounds and ears were examined at intervals. Cases with pulmonary localizations were studied roentgenologically at intervals of one month, and those with laryngeal ones were laryngoscoped weekly. The patients were followed up after discharge and whenever possible autopsy was done in fatal cases.

There were 25 cases of isolated meningeal tuberculosis, 17 of associated meningeal tuberculosis, 5 of pulmonary miliary tuberculosis, 11 of laryngeal tuberculosis, and 11 of various localizations, and all cases are reported in some detail. There were 11 autopsies; 8 of them concerned cases of meningeal tuberculosis which terminated fatally in spite of streptomycin treatment which had been incomplete or delayed in some of them. With respect to topography of the lesions, these cases showed a greater variety than untreated cases; the latter usually show predominance of the inflammatory process in the interpedunculochiasmatic fossa with extension to the initial portion of the sylvian fossa, the cerebral peduncles and the proximal portion of the upper cerebellar worm, while in the cases under consideration the cisterna of the interpedunculochiasmatic fossa frequently showed lesser involvement and the leptomeninges of the pons and medulla oblongata often showed more intense involvement.

The sylvian fissure and the leptomeninges covering the circonvolutions at the base of the frontal lobes, on the other hand, showed scanty infiltration with exudate. The inflammatory process showed a predominantly productive character, while before streptomycin treatment, an exudative character prevailed particularly in young individuals, and a productive type was reported as a variety of its own. Reparative processes reached a discretely advanced degree although complete transformation into dense adult fibrous cicatricial tissue was not observed. In some cases the process extended from the leptomeninges to which it is normally limited, to the dura mater corresponding to the clivus resulting in dense adhesions between the two layers. Another interesting feature was the unusual degree of participation of the basal vessels in the process; while the granulomatous tissue invaded the media from the outside the process of proliferative endoangiitis with a histologically nonspecific character and well known in this affection reached unusual intensity, causing marked narrowing of the lumen. There was extensive involvement of the nerve substance, and in this respect too the differences from untreated cases were purely quantitative, as tuberculous meningitis is

always associated with encephalitis; however, in the cases under consideration, the cufflike perivascular lymphoid infiltrations extended to a greater depth, particularly at the level of the floor of the third ventricle, but also at that of the pons and elsewhere. Perhaps a nonspecific lesion due to propagation of catabolites from the focus of inflammation along the perivascular sheaths was dealt with, and this may account for certain symptomatologic aspects in some cases. Hydrocephalus of variable intensity was constantly found, and the plexus choroideus, and less frequently the ependyma was involved. The author could not confirm the frequency of nodular involvement of the dura mater, involvement of the spinal meninges, and foci of malacia of the brain substance, claimed by others in streptomycin-treated tuberculous meningitis. The most obvious and satisfactory explanation of the differences from untreated cases is that of the time factor; attenuation of the process by the antibiotic permitted a subchronic or chronic course which had been unknown before, or had been exceptional at most. The interplay between the antibiotic which favors the natural healing tendencies and the disease itself may account for the polymorphism of the lesions, their extension, and the predominantly productive character. The last 3 autoptic cases were of particular significance.

In the first of these cases the anatomical impression was that the exudative tuberculous process had been partially or totally absorbed, the latter with respect to the lungs, leaving the anatomical substrate of the affected organs intact. From an epicrisis of the clinical course and the anatomical findings it may be concluded that pulmonary miliary tuberculosis and external leptomeningitis were cured by the streptomycin treatment, the latter only incompletely, while ependymitis and encephalitis proved resistant to the antibiotic. The second case showed a series of tuberculous episodes following the primary infection, to be reconstructed epicritically as follows: pleurisy, nodular hematogenous dissemination in the pulmonary apexes and the brain with a chronic fibrocalcareous character, chronic bone tuberculosis of the os ischium, pulmonary and subsequently meningeal miliary tuberculosis, both controlled by streptomycin treatment, and simultaneous appearance of an exudative retroclavicular pulmonary focus with rapid cavity formation, and of foci of osteitis at the level of the sternum, and finally of coxofemoral arthritis. The last case was particularly interesting as the patient succumbed 10 months after admission to an annular infiltrating cancer of the gastric antrum with metastases in the liver and the regional lymph glands and neoplastic peritonitis; an ulcer with signs of stenosis had been suspected clinically and a gastroenteroanastomosis had been performed. The cure of the miliary and meningeal tuberculosis by the streptomycin treatment was demonstrated by the lack of active inflammation at the level of these organs and the absence of functional disturbances.

The total mortality was 14 cases or 21 per cent, but 4 patients died within 10 days after admission, and 1 left the hospital after 4 days, so that the mortality among 64 sufficiently treated cases was only 15.5 per cent. The mortality rate in meningeal tuberculosis, alone or associated with miliary tuberculosis was 26.3 per cent, and that in isolated meningeal tuberculosis 30 per cent. Early treatment, and particularly early intraspinal treatment, seems of the greatest prognostic significance. The mortality rate was higher in the cases in which the tuberculous nature of the process was not immediately recognized, and lower in the cases in which the meningeal tuberculosis supervened in the course of miliary tuberculosis where the diagnosis was already established. In miliary tuberculosis systematic examinations of the spinal fluid will make it possible to diagnose meningeal involvement at the earliest moment.

Toxic manifestations were rare. One patient showed a transitory erythematous affection and 7 showed acoustic disturbances; the latter subsided virtually completely in 3 cases and were limited to one ear in 3, while 1 patient became completely deaf. In the latter case, because of the particularly serious condition, 200 mg. instead of the usual 50 mg. were injected intraspinally for several days; the deafness may have been produced by the meningitis as well as the antibiotic. Out of 21 cases examined ophthalmoscopically, miliary tu-

bercles were found in 7, 2 of isolated meningeal and 5 of combined meningeal and miliary tuberculosis.

No patients were found to become unresponsive to the antibiotic, and recurrences of tuberculous meningitis were observed in only 2 cases, 1 with regression and the other terminating fatally. In some of the fatal cases the streptomycin showed from the beginning scanty or no effect; apparently some strains are primarily resistant to the antibiotic. Systematic combined clinical and laboratory studies will be required to solve the problem of streptomycin resistance.

One of the causes of death in meningeal tuberculosis is a blockage with resulting internal hydrocephalus. In 3 cases drainage of the ventricle was carried out but unsuccessfully. However, since suboccipital puncture has been widely used, severe blockage and internal hydrocephalus have no longer been observed, although it cannot as yet be said that there was a relation of cause and effect between these two facts. There were no deaths in miliary tuberculosis without meningitis. The results were astonishing in laryngeal tuberculosis, with total regression of all manifestations in 10 of the 11 cases, and improvement in the residual case where treatment had to be discontinued after six weeks as the patient left the hospital. Some of these patients are still under pneumothorax treatment for their pulmonary tuberculosis; extralaryngeal localizations must be treated persistently in order to prevent recurrences. In inhalation treatment better results were obtained with an apparatus which does not produce intense atomization of the streptomycin; fine atomization seems to favor penetration into the depth of the bronchial tree but to make deposition on the tuberculous pharyngolaryngeal manifestations less easy. It was found inadvisable to use oxygen as vehicle for the streptomycin, as it produces secondary irritation which partly neutralizes the therapeutic effect of the antibiotic. In the author's experience streptomycin has little effect on cavitary phenomena; it does neither heal nor prevent them.

With respect to spinal fluid findings, the author points out that reticulum formation is an expression of high activity and therefore severity of the meningeal process; it is not related to the total protein concentration but to the quality of the protein substances, and particularly to the presence of fibrinogen, and is of considerable prognostic significance. No simple and clinically applicable quantitative method of fibrinogen determination is available. In the presence of a low block, at the level of the spinal cord, the fluid obtained by spinal puncture may contain more protein than that obtained by suboccipital puncture, while the number of cellular elements is equal in both fluids. If this fact is neglected, prognostic significance may wrongly by attributed to the cytoalbuminoid dissociation of the fluid obtained by lumbar puncture alone. Such dissociation is an early sign of blockage and internal hydrocephalus only if it is found in the suboccipital fluid as well as in the spinal one.

Combined streptomycin and paraamino salicylic acid treatment was used in 12 cases, and this number is too small to permit definite conclusions particularly as patients with various types of tuberculosis were included. However, the author is under the impression that this combination has certain advantages, both in initial and in chronic forms with cavities. In 1 case this combination resulted in rapid development of the lesions towards fibrosis, with rapid improvement of the general condition. It also seemed that prolonged treatment with paraamino salicylic acid at home after discharge from the hospital definitely favored consolidation of the favorable results obtained with streptomycin alone or with its combination with paraamino salicylic acid.

Over a period of seven months after the one year period dealt with above, another 35 cases were observed; namely, 25 of meningitis, 4 of miliary tuberculosis, 1 of laryngitis and 5 of various tuberculous manifestations; 1 patient with meningitis died within six days, and there were 7 subsequent deaths, amounting to 20.58 per cent. All deaths belonged to the group of meningitis, and the mortality of this group was 28 per cent. Dihydrostreptomycin was used in this series and it seems to cause intolerance on intraspinal injection more frequently. During this second period 2 cases of recurrence of tuberculous meningitis, involving patients of the first period, were observed; 1 patient recovered

rapidly, while the other succumbed rapidly after having developed severe paralytic symptoms of a central type. On autopsy, the meninges were almost normal, while the cerebral arteries showed severe alterations to which vast cerebral malacias responsible for death must be attributed. Thorough histological studies were not possible. Some patients showed persistent hypertension of the spinal fluid after complete normalization. In patients with a low blockage appreciable disturbances are not always present.

In some cases roentgenotherapy of the spine led to complete restoration of the spinal canal. A characteristic caudal syndrome with motor and sensory disturbances of the lower limbs, and also trophic and sphincter disturbances, persisted in only 1 case after complete normalization of the spinal fluid, probably on the basis of extensive firm fibrous adhesions at the level of the terminal portion of the spinal cord and the nerve roots originating from it. Finally, some patients, discharged cured after tuberculous meningitis developed intense progressive obesity; determination of the basal metabolic rate revealed no appreciable thyroid hypofunction and in all likelihood the obesity must be attributed to a meningoencephalitic process involving the pituitary-diencephalic region.

The Value of Enteric-Coated Aspirin— Talkov, Robert H., Ropes, Marian W. and Bauer, Walter — *New England Journal of Medicine*, 242: 19 (January 5) 1950.

"Because of its analgesic value, acetylsalicylic acid (aspirin) is used extensively. In the treatment of certain rheumatic disorders, maximal dosage over long periods is frequently necessary if optimal control of pain is to be attained. However, in consequence of the local irritation of the gastric mucosa, one frequently encounters the distressing symptoms of heartburn, nausea, epigastric fulness and pain, anorexia and vomiting; rarely, hematemesis occurs." In an attempt to avoid these symptoms the writers employed an aspirin tablet with an enteric coat that would resist dissolution in the stomach and thereby prevent actual contact between the drug and the mucous membrane. The effects of the administration of this preparation to 32 patients are reported.

"Preliminary qualitative tests using ferric chloride as an indicator have shown that the time of appearance in the urine is only slightly delayed as compared with that of ordinary aspirin. The analgesic effect was generally apparent in 20 to 40 minutes, and all but 2 of the patients estimated it to be equal with both forms. Twelve subjects who were able to tolerate regular aspirin without untoward gastric symptoms were given sufficient amounts to produce the central toxic effects of dizziness, tinnitus or deafness. Later, an equivalent dose of enteric-coated aspirin was followed by the same symptoms. These observations indicate that the enteric coat does not materially alter the fundamental pharmacologic effects of the acetylsalicylic acid. Intolerance (epigastric fulness and anorexia) to the enteric coat was suggested in only 1 patient.

"Gastric symptoms of varying intensity, resulting from the ingestion of common aspirin, were present in 20 patients. The degree of intolerance was determined in each case by the administration of 0.6 or 1.0 Gm. (10 or 15 grains) every four hours, the total daily intake gradually being augmented by an increase in the frequency of administration to every three and two hours until symptoms became evident. The majority tolerated from 2.0 to 3.3 Gm. (30 to 50 grains) a day as a maximum, but the extremes observed ranged from as little as one 0.3 Gm. (5 grains) dose to 5.3 Gm. (80 grains). In subsequent studies occasional patients were able to tolerate as much as 10.0 Gm. (150 grains) per day. The substitution of enteric-coated aspirin was followed by complete relief of gastric symptoms in all 20 cases, and in practically every case it was possible to increase the total daily intake of acetylsalicylic acid by 1.3 to 2.6 Gm. (20 to 40 grains) and thereby to provide greater relief of pain. The maximum dosage was determined not by gastric symptoms but rather by the development of toxic symptoms of central origin. Previously, many of this group had, with variable success, taken soda or food with their aspirin to avoid heartburn, nausea and so forth. Invariably, they preferred the enteric-coated tablet because of the

convenience and greater efficacy resulting from increased tolerance.

"Melena or hematemesis, resulting from regular aspirin, was not observed in this small series. However, it has been amply demonstrated that gastric hemorrhage may be a complication of acetylsalicylic acid therapy. If this untoward effect is suspected or has occurred, the administration of enteric-coated acetylsalicylic acid is indicated. Its use is recommended also in patients with peptic ulcer, who frequently are unable to take aspirin without increased gastric distress." The writers have treated 3 such patients with rheumatoid arthritis with good results.

"Additional evidence of the effectiveness of these tablets has been obtained by observation of total salicylic concentrations in serum. In 2 patients the levels were essentially the same on daily doses of 4.0 Gm. (60 grains) of enteric-coated aspirin for one week as they had been on similar doses of regular aspirin (8.0 and 10.6 mg. per 100 cc. as compared with 6.2 and 14.6 mg.). In 3 patients serum salicylate levels while enteric-coated aspirin was being given in sufficient dosage to produce toxic symptoms of central origin were of the same magnitude as those obtained after similar doses of plain aspirin (19.6, 26.9 and 26.9 mg. per 100 cc. as compared with 19.2, 21.4 and 22 mg. per 100 cc.)."

Acute Lymphocytic Choriomeningitis. A Study of 21 Cases — Green, William Roy, Sweet, Lewis K., and Prichard, Robert W. — *Journal of Pediatrics*, 35: 688 (December) 1949.

In order to define more clearly the clinical picture produced by the disease, the writers are reporting their experience with 21 proved cases of acute lymphocytic choriomeningitis.

"These patients were studied on the Communicable Disease Service of the Gallinger Municipal Hospital between July 1, 1938, and June 30, 1948. They include all patients for whom the diagnosis was conclusively established in this 10 year period."

"The ages of these 21 patients ranged from 6 to 39 years. Four patients were in their first decade, 6 in their second, 3 in their third, and 8 in their fourth. The distribution according to sex was 14 females and 7 males, a definite preponderance of females which has not been noted before. The 4 patients under 10 years of age were divided equally between the sexes. The preponderance of adult female patients lends support to Armstrong's theory of the mouse reservoir of virus in the transmission of the disease since adult females probably would have closer contact with mice and their excreta in the home than would males. The racial distribution was 11 Negroes and 10 whites which corresponds fairly well with the racial distribution of patients seen in this section of the hospital."

"The patients came from many social and economic levels, and from varied types of dwellings, from hovels to middle-class suburban homes." Three of the patients were found to have mice infected with the virus of lymphocytic choriomeningitis in their dwellings. "All 3 of these patients yielded the virus from their spinal fluid.

"Headache was the most common single complaint, and was present in all instances. There was no particular localization, though it was frequently described as being generalized, with some accentuation 'behind the eyes.' Its intensity is marked. Headache persisted for an average of 12.6 days, the longest being 30 days (2 cases), and the shortest 3 days. This symptom frequently was relieved entirely, though temporarily, by lumbar puncture.

"Nausea and vomiting were present on or before admission in 16 of the 21 patients, and in 3 instances continued after admission to the hospital. It is possible that the decrease in intracranial pressure resulting from the lumbar puncture may have relieved the cause of this symptom in most of the patients.

"Photophobia was present in 6 patients, and persisted after admission for several days. It was not related to the fever, occurring when the patient was afebrile. Funduscopy was normal in these patients. The only patient in the series with papilledema did not complain of photophobia."

Under grippal symptoms, the writers have grouped nonspecific symptoms such as sore throat, malaise, generalized aches and pains, and anorexia. All of their patients complained of feeling bad, and anorexia usually was present at one time or another during the course of the disease.

Ten of the patients had definite symptoms of grippe at the onset of their illnesses. "Eight of these were treated as such for five or more days before the headache and other complaints became so severe that hospitalization was sought or recommended. Four of these 10 patients had been ill for periods of from one to six months with vague complaints, such as mild headache, weakness, and lassitude. They had been diagnosed as 'nervous exhaustion,' or 'psychoneurosis' by their physicians. Each of the 4 had an accentuation of their symptoms a few days before admission." Eleven patients presented an onset typical of that seen in purulent meningitis. "A clearcut history of sudden appearance of meningeal symptoms, which progressed until hospitalization was sought, was obtained from these patients." About 50 per cent of the patients, therefore, had grippal symptoms before the onset of meningitic involvement.

"Fever was present on admission in all patients except 1, whose temperature was 99° F. The fever usually was of the sustained variety, disappearing by lysis. . . . During the course of the disease in the hospital the temperatures varied from 100 to 105° F., averaging 102.3° F. The fever persisted for periods of from 1 to 10 days, the average being 4.4 days. The pulse rate was in keeping with the temperature level.

"All patients presented stiffness of the neck on admission. The nuchal rigidity was moderately severe, usually being classed as two plus or three plus. The Kernig and the Brudzinski signs were positive in 16 patients."

Of the 21 patients, 6 were rational on admission; the others ranged from "cloudy" to "comatose," in the words of the admitting examiner. "One had experienced a convulsion. All appeared acutely ill." Since the word "benign" unfortunately has been incorporated into the nomenclature of this disease, the writers feel that it is particularly important to stress the severity of the illness that may be seen among these patients.

"One patient complained of urinary retention which persisted from the sixth to the eighth day of her illness. Other complaints, each in a single instance, were syncope, vertigo, abdominal pain, tremor, and insomnia."

"The admission cell count appeared unrelated to the degree of temperature and fell to normal long after the temperature had reached normal limits. The total count on admission varied from 142 cells to 3,370 cells, the average being 1,179 cells. The most striking finding in connection with the cell count was the observation that a high cell count increased the likelihood of isolating a virus from that specimen. Of the 15 fluids which yielded the virus, only 3 had cell counts below 1,000, containing 840, 530, and 210 cells, respectively. Also, fluids obtained earlier in the disease are more likely to be virus-containing than later specimens." Eleven of the virus-containing fluids were obtained in the first week of their disease, the remaining 4 being collected on the eighth, tenth, fourteenth, and fifteenth day of illness, at which time they had high cell counts, 1,200, 1,100, 530, and 3,370, respectively.

"The name of the disease indicates the usual finding in the differential cell count." The spinal fluid from all patients contained from 90 to 100 per cent lymphocytes, none lower.

"The spinal fluid dextrose at initial and subsequent examinations was normal on all specimens from 14 patients. Seven patients presented one or more readings with decreased dextrose content (30 mg. per cent or less). Five patients . . . . showed a definite decrease in the initial spinal fluid dextrose . . . . but were found to have normal spinal fluid dextrose at subsequent examinations. In 2 patients, extremely interesting decreases in the level of this substance were noted. In 1 patient the admission spinal fluid contained 3,370 cells, and by qualitative test there was no reduction of Benedict's solution in any of the five tubes indicating a dextrose content of 10 mg. per cent or less. On the following day there was again no dextrose by qualitative test, the cell count being 1,625 at that time. Two days later the cell count was 699, and the dextrose was normal, remaining so on the two following examinations at five to seven day intervals. Another patient on admission showed 840 cells, dextrose 79 mg. per cent; four days later her cell count had risen to 2,300 and there was no dextrose by the qualitative test. The following day the absence of dextrose was again demonstrated with a

cell count of 1,460. Two days later her cell count was 1,890, her spinal fluid dextrose 50 mg. per cent, her blood sugar 94 mg. per cent. On the two following taps, with cell counts of 340 and 21, normal spinal fluid dextrose was found. Both of these patients had the virus isolated from their spinal fluids.

"In 10 instances out of the 16 in which protein determinations were done on the initial spinal fluid specimen, the protein value was above 100 mg. per cent. In 12 patients this value was exceeded sometime during the course of the disease. Values ranged from 20 to 700 mg. per cent, and it is worth noting that late in the disease, after the cell count had returned to normal, some patients were found to have a protein level above 100 mg. per cent."

In 2 patients the fluid from which the virus was isolated also gave a doubtful, and a weakly positive, reaction, respectively, to a serologic test for syphilis. "The specimens giving these reactions also showed a first zone colloidal gold curve of the type commonly called 'paretic.' Succeeding examinations in both patients revealed normal reactions, the examination being repeated twice again in each case. In the first patient, blood serologies ranged from two plus to four-plus, and a competent syphilologist who examined the patient opined that hers might well be a case of a positive reaction due to nonsyphilitic disease. She did not return for the suggested follow-up examinations, and her exact status with regard to syphilis is unknown. The second patient had negative blood serology."

The determination of spinal fluid chlorides was performed only sporadically in the writers' patients, since they feel that little is to be learned from this test on the cerebrospinal fluid. "The chloride content of the spinal fluid seems to bear a direct relation to the chloride level in the blood, and it is lowered by any condition affecting the blood chloride level, such as the vomiting and excessive sweating seen in many diseases, especially the meningitides."

The blood picture in 15 of the 21 patients was normal, the white count varied from 4,800 to 10,000, with a normal differential count. "Two patients had pneumonia; 1 had a white blood count of 25,800, the other a count of 12,850 with the usual polymorphonuclear response. Two patients had cervical adenopathy and white blood counts slightly elevated. One 9 year old boy had a white count of 4,100 with an increase of lymphocytes."

The erythrocyte sedimentation rate was performed on only 4 patients, and all were normal.

Except for traces of albumin during their febrile period, the urines of most patients showed nothing remarkable or specific.

"The exact diagnosis of lymphocytic choriomeningitis is based on the isolation of the virus from the spinal fluid of patients in the acute stage of the disease, and/or demonstration of an increase in the titer of antibody against the virus following the acute illness in question." The writers' patients all fulfilled these criteria, 15 yielding the virus, the remainder showing a definite rise in neutralizing antibody titer.

"The differential diagnosis of lymphocytic choriomeningitis is complicated by the fact that there are a host of conditions that may produce a serous meningitis which is quite similar in clinical manifestations to that caused by the virus of lymphocytic choriomeningitis. Even in the best circumstances the specific diagnoses of those that are due to agents other than syphilis or tuberculosis usually are made with difficulty, if at all."

"In the group of diseases due to viruses, if the season for poliomyelitis is in progress or in view, this disease must be kept in mind until proof of some other etiology is available. Even if a patient is admitted without evidence of the type of paralysis that is characteristic of poliomyelitis he should be examined daily for evidence of muscular weakness. Usually the total cell count in the spinal fluid is lower, and the differential count usually shows not over 70 per cent lymphocytes. In some patients, however, there may be over 90 per cent lymphocytes. The shift from polymorphonuclear cells to lymphocytes, as seen frequently in poliomyelitis, has never been observed in lymphocytic choriomeningitis. The various forms of encephalitis are diagnosed specifically only by virologic study, and present a widely overlapping clinical

picture, with signs of diffuse involvement of the central nervous system. The history must be meticulously taken on the subject of exposure to contagious disease. Thus a patient who has no clinical evidence of mumps may have a mumps meningoencephalitis, the etiology of which might go unappreciated if a history of exposure were not obtained. The mumps skin test, and finally, mumps complement fixation antibody determination will establish the diagnosis firmly. In general, serous meningitis associated with the exanthemas and vaccinia is accompanied by a lower cell count than most of the cases of lymphocytic choriomeningitis and is diagnosed by the other manifestations of the disease. Virus infections other than those commonly associated with exanthemas may be present in the central nervous system; for example, infection with the virus of lymphopathia venereum. The virus of herpes simplex, which is widespread in the human system, rarely invades the central nervous system, and may cause an illness clinically indistinguishable from lymphocytic choriomeningitis. As yet unknown is the cause of the central nervous system involvement seen in infectious mononucleosis, where presumptive evidence strongly points to a virus as the etiological agent. The blood picture and the Paul-Bunnell test are of aid here.

"Rarely one sees a purulent meningitis that in its early stages may assume a serous form; that is, the pleocytosis in the spinal fluid is predominantly lymphocytic." The writers have seen *Hemophilus influenzae* meningitis appear in this fashion on several occasions, the diagnosis being made by identification of the organism on smears or cultures of the cerebral spinal fluid.

"The differentiation of tuberculous meningitis from lymphocytic choriomeningitis may be extremely difficult. As a rule, the cerebrospinal fluid dextrose is lowered in tuberculosis, but this finding may come late in the disease, and as shown above even relatively persistent reduction of cerebrospinal fluid sugar does not eliminate the possibility of lymphocytic choriomeningitis. The protein and chloride content of the spinal fluid are of little differential value. The total cell count usually is less in tuberculosis, and the differential count usually shows a smaller proportion of lymphocytes. However, the total cell count in tuberculous meningitis frequently numbers well over 200, and the differential count may show over 90 per cent lymphocytes. The definite differentiation of these two conditions can be made most satisfactorily by the demonstration, in patients with tuberculous meningitis, of tubercle bacilli in the spinal fluid, or of tuberculosis elsewhere in the body. Since tuberculous meningitis frequently is a manifestation of hematogenous tuberculosis, the examination of the bone marrow by the technique of Katz, Lifschutz, Milloff, Geiger, and Marshall has proved to be extremely useful in establishing the diagnosis of tuberculous meningitis.

"Spirochetal infections usually are diagnosed readily. Serological evidence of syphilis together with a suggestive history will permit diagnosis. Weil's disease is accompanied by icterus which may result in xanthochromia of the spinal fluid. Agglutination reactions are essential in the diagnosis of this disease.

"Mastoid disease and brain abscess may produce serous meningitis by irritation of the contiguous meninges, and are revealed by physical examination and localizing neurological signs.

"Lead poisoning may produce a chemical meningitis. Typical blood changes and abnormalities in x-rays of the long bones showing a deposition of lead at the growing ends lead to a correct diagnosis. Intrathecal medication, especially with therapeutic serums, will produce a meningeal reaction, as will iodized oil or air which is allowed to enter the cerebrospinal system.

"The meningitides due to fungi are poorly understood, with the exception of that due to *Cryptococcus hominis*. Occasionally the Cryptococcus may resemble a lymphocyte, and if any suspicion concerning morphology of the cells arises, further test, such as the India ink test, should be done."

"Toxoplasmosis affecting the central nervous system is most frequently seen in infants and is characterized by convulsions and a picture suggestive of encephalitis or hydrocephalus. The spinal fluid may contain from 20 to 2,000 cells. X-ray evidence of calcification inside the skull, with demonstration of agglutinating and com-

plement fixing antibodies against the toxoplasma organism aid in diagnosis. Examination of the fundi is often of great help in these cases. Serous meningitis has been seen in approximately 1 per cent of patients with scarlet fever at this hospital, the cause being unknown. The meningitis is indicated by the recrudescence of fever after the disease seems to be abating, accompanied by signs of meningeal irritation that often are minimal. It is not related to purulent complications of the disease. The spinal fluid findings are almost identical with those of choriomeningitis, though in general the total cell count is somewhat lower."

In 19 of the 21 patients the course of the disease has been short, self limited, and benign, in the sense that there were no residuals nor any deaths. "The average hospital stay for this group of patients was 27 days." Two of the patients pursued courses that were essentially the same as the others, but developed severe and prolonged headaches, with evidence, on readmission for these complaints, of increased intracranial pressure which required periodic spinal punctures for relief. "One man was heard of three years after his initial hospitalization, still unable to work steadily because of his headaches. The second patient who developed this complication was known to have had headaches for several months. He was last heard of three years after his initial hospitalization, complaining of low back pain while in an Army camp; no mention was made of headache at that time. Since he had had a portion of a spinal puncture needle broken off in his paravertebral muscles, with subsequent surgical removal, the back pain cannot be assigned to lymphocytic choriomeningitis. The headaches probably were a result of the meningitis.

"The prognosis as to life and aftereffects is excellent." The writers have seen no deaths in this disease, and complications only as noted.

"The treatment of this disease is completely symptomatic, and consists of complete bed rest and analgesics, with fluid and diet control as indicated by the patient's symptoms and general condition. The most important item is the complete bed rest." The 2 patients who developed headache were among the first patients in this series. "Both were allowed to get out of bed when their temperature fell and when they felt as though they would like to get up, at which time their pleocytosis had not subsided. The unfortunate outcome of their cases has led to the policy, perhaps based on coincidence, of keeping patients with meningitis on bed rest in the hospital until the cerebrospinal fluid has receded almost to normal, then to remain in bed at home for four to six weeks following discharge." Since this regime has been enforced the writers have not encountered any complications in these patients.

"Two patients had pneumonia complicating their disease. They were treated with sulfonamides and responded satisfactorily with no apparent difference from the usual course of such infections."

The Treatment of Genitourinary Tuberculosis with Streptomycin Alone — Lattimer, John K., Amberson, J. Burns and Braham, Stanley — *Journal of Urology*, 62: 875 (December) 1949.

"Two hundred and fifty-three cases of genitourinary tuberculosis have now been treated with streptomycin by the Veterans Administration, Army and Navy Research Group. As a result of this experience, a few generalizations can now be made concerning the questions of optimum dosage and limitations of the drug."

"There are several possible criteria of improvement in renal tuberculosis: (1) the disappearance of the tubercle bacilli from the urine; (2) the arrest of the destructive process; (3) loosening of strictures; (4) fibrosis and/or calcification; (5) clinical improvement of symptoms; and (6) the disappearance of pyuria. The most demanding criterion is the disappearance of tubercle bacilli from the urine, and this study is, therefore, presented in terms of the per cent of cases successfully converted from positive to negative for tubercle bacilli in the urine."

"It has been suggested that the increased fibrosis, hastened by streptomycin, is a sign of healing. Unfortunately this rapid fibrosis may have disastrous effects on badly infected ureters, causing them to contract and become occluded.

"If such a ureter serves a solitary kidney, a nephrostomy must be done." The

writers have seen this happen in 2 out of 50 cases with renal tuberculosis. "It has also been suggested that calcification is a sign of healing, but six of the seven renal lesions in this group which contained calcium failed to be converted to negative. It was noted that even when the tubercle bacilli disappeared from the urine, pyuria continued in most of the cases."

"The most effective dosage regimen against active ulcerating renal lesions when streptomycin alone was used, was 0.3 Gm. every four hours day and night for 120 days. As the dosage or time of treatment was lessened, the effectiveness decreased. Forty-two day regimens were inadequate.

"Large renal lesions responded poorly. Most patients with renal tuberculosis were not discovered until their lesions were large enough to be definitely visible in the pyelogram. Any lesion which was visible in the pyelogram probably contained necrotic and fibrous tissue and was classified as a large renal lesion, even if only one calyx was involved. In this group of patients tubercle bacilli disappeared from the urine in only 25 per cent of the cases although in many additional instances the progress of the disease was apparently slowed or halted. Surgery was preferred for such renal lesions if the active disease was unilateral.

"Small renal lesions responded well. The rare tuberculous kidney lesion which was discovered by means of a positive ureteral urine before there was a visible pyelographic lesion probably contained less necrotic and fibrous tissue." In the writers' pilot series, 8 out of 10 such kidneys became consistently negative and the remaining 2 are probably negative.

"Narrowing of the ureter was seen in a few cases. In 1 instance where the narrowing was so severe that it caused shortening of the ureter, the treatment with streptomycin appeared to hasten the fibrosis, with further shortening and constriction of the ureter, resulting in the complete obliteration of the tube. Caution must be exercised in the treatment of solitary kidneys with severe ureteritis. In other cases where the obstruction appeared to be the result of superficial ulcerations or edema without shortening or fibrosis of the ureter, the action of streptomycin was distinctly beneficial. It caused the stricture to loosen and the hydronephrosis and hydroureter to disappear as treatment progressed. Here again superficial lesions appeared to improve while advanced lesions were not benefited."

"Superficial bladder ulcerations healed rapidly under streptomycin treatment. They were greatly improved in four weeks and in many cases completely gone at the end of eight weeks. Symptoms improved rapidly as the areas of superficial cystitis receded. Patients who had had extreme frequency and urgency were able to get more sleep with the lengthened period between voidings. As a result, the patients who were debilitated regained their weight. These findings were supported by biopsies from superficial ulcerations which showed the disappearance of leukocytic, epithelioid, and round cell infiltration after the ulcerations healed. Residual cystitis after nephrectomy, or cystitis secondary to the overflow of organisms from a tuberculous prostate, was treated with streptomycin until the cystitis was gone, so as to prevent contractures of the bladder. Patients whose bladders showed superficial acute lesions, with capacities of only 300 cc. frequently saw their capacities increase to 500 cc. by the end of treatment. It was noted that the bladder lesions recurred if the kidneys broke down and again became positive for tubercle bacilli." It was also the writers' impression that cystitis cleared more rapidly when the drug was given around the clock in doses every 4 hours, rather than in doses every 12 hours. "It is reasonable that a urinary level which is maintained throughout the 24 hours might conceivably have a greater beneficial topical effect upon the bladder lesions than that from intermittent therapy.

"Deep-seated fibrous contractures of the bladder were not helped by streptomycin; where fibrosis of the bladder was present before treatment, it was still present after treatment. Bladder capacities which averaged 50 cc. before treatment, improved very slightly to about 100 cc. but never improved significantly."

"Prostatic and epididymal tuberculosis did not respond sufficiently well to merit the use of streptomycin except where severe cystitis had resulted from local extension of the lesion into the bladder. Epididymal tuberculosis was preferably

treated by surgery, accompanied by three weeks of streptomycin."

It is the writers' present policy to defer treatment for tuberculous nodules in the prostate which are causing no trouble. "If ulceration in the posterior urethra and onto the bladder surface occurs, with severe symptoms and the possibility of a bladder contracture, streptomycin is given and kept up until the symptoms are controlled or resistance to the drug develops."

"Excision appeared preferable to streptomycin treatment for any lesion where there was a large amount of necrotic tissue. In cases with unilateral active, progressive tuberculosis of the kidney, the kidney is now excised as soon as it has been determined that the remaining kidney shows no activity in the form of tubercle bacilli or pus in the urine. Excision is also the treatment of choice for active tuberculous epididymitis. Both nephrectomy and epididymectomy are accompanied by a short course of streptomycin." It is the writers' practice to give 0.5 Gm. streptomycin every 12 hours for a period of 3 weeks following any operation on a tuberculous organ. This dosage is still experimental but the writers start the treatment two or three days before operation and continue it for the balance of the three weeks after operation. They do not exceed three weeks of treatment because resistance to streptomycin is more prone to develop after three weeks. Pending the development of additional tuberculostatic drugs, they believe that it is extremely important not to squander 120 days of streptomycin upon inactive foci which may not respond. "It is important not to make the patient's organisms resistant by administering 120 days of streptomycin after the active foci have been excised. The three weeks' course is aimed at the possible prevention of hematogenous dissemination." It is the writers' experience that this course of medication does not protect the patient against a wound infection at the site of operation, if tubercle bacilli are spilled in the wound in any quantity. Because of this fact it is the writers' practice to leave the ureter or the vas deferens intact until the wound is entirely closed. "The tube is then clamped and cut outside the closed incision. After five days the stump is permitted to drain onto the skin until it withers and dries up." It has not yet been determined whether or not three weeks of streptomycin is sufficient to do any good at all in advancing the healing of the dormant tubercles which the writers presume to be present in the remaining good kidney. It seems to them to be unwise, however, to give a longer course at this time, aimed at inactive lesions, since it would make the organisms resistant and thus have squandered the patient's only therapeutic weapon, should he later develop the meningitis or renal tuberculosis which kills so many of these people.

"On the 2 Gm., 120 day regimen, all of the 25 pilot patients developed some permanent loss of vestibular function as measured by caloric tests. Some of the patients were markedly dizzy and some patients were not dizzy at all. All of the patients showed a permanent vestibular loss which came on after about 30 days of treatment. After treatment was stopped, the patient's dizziness began to improve and with the addition of eye exercises and coordination exercises, the ataxia has been compensated for by almost everyone. The corrective exercises employed were designed to improve the efficiency of the visual and muscle, joint and tendon senses in maintaining equilibrium. Most of these men have compensated for the vestibular loss so well that they are not handicapped. Hearing loss was not a prominent feature on this regimen. Rises in blood urea nitrogen were not severe, although in some cases there was a slight transitory rise to about 40. Since many of these patients had only one fragment of a solitary kidney remaining and since their kidney function did not suffer, it was concluded that this dosage was not markedly toxic for the kidney. In a few patients, skin rashes became severe and in 2 of 24 cases, compelled curtailment of the treatment. When the dosage was reduced to 1 Gm. for 120 days, toxicity was markedly reduced but so was the effectiveness of the drug against the tubercle bacilli. Intermittent and repeat courses of streptomycin were less toxic than continuous treatment."

"Tubercle bacilli from all these patients were sensitive to streptomycin at the beginning of treatment. In those cases which continued to show tubercle bacilli in the urine in spite of treatment, there was a

marked rise in resistance as time went on. It should be recorded here, however, that even after test tube resistance had developed, symptoms were sometimes improved by repeated additional courses of streptomycin."

Poison Ivy. A Summary of 100 Cases Treated with Aqueous (Alum-Precipitated Pyridine) Extract — GAILLARD, G. EVERETT — *Journal of Allergy*, 21: 55 (January) 1950.

"A total of 113 patients, hypersensitive to poison ivy, were treated with pyridine ivy extract during the years 1945, 1946, and 1947."

"The pyridine ivy extract is simple to use, produces no discomfort, and is very stable."

"The cases selected for this study were all obtained from a private practice, confined wholly to the treatment of allergic diseases. All were referred to the office for the treatment of poison ivy, or were patients regularly seen in the office for the treatment of other allergic diseases who requested treatment for poison ivy. All had either clinical poison ivy or a recent clinical history of poison ivy of moderate to intense severity. In the majority of cases, the attacks had been repeated for several years. Most of the patients were children residing in suburban or semirural areas."

"Patch tests with serial dilutions of freshly prepared poison ivy extract of both the alcoholic and aqueous alum-precipitated pyridine variety were performed simultaneously on 36 of the patients. These cases were selected at random with no regard for their hypersensitiveness, other than their clinical history or previous clinical findings. The patch tests were performed in the usual manner, employing the outer side of the arm as the test site. All negative tests were repeated with extracts of proved potency.

"Twenty-three of these patients gave positive reactions to the alcoholic extract in the 1:1,000 dilution, while in the same group, 10 patients responded positively to the pyridine-aqueous extract in the 1:1,000 dilution; and 12 to the 1:100 dilution. One failed to respond at all to the aqueous extract. Seven of these patients gave positive reactions to the alcoholic extract in the 1:100 dilution, while in the same group, 3 patients responded positively to the pyridine-aqueous extract in the 1:100 dilution and 3 to the 1:10 dilution. One patient failed to respond at all to the aqueous extract. Two of these patients gave positive reactions to the pyridine-aqueous poison ivy extract in a 1:100 dilution and failed to respond at all to the alcoholic extract. Four patients yielded negative patch tests to both extracts. In other words, about one half of the patients who were positive to the patch tests with the alcoholic ivy extract were also positive to the pyridine ivy extract in the same serial dilution, while the other half required a lesser dilution of the pyridine ivy extract to elicit a positive reaction.

"The findings of lesser activity by patch testing with the pyridine ivy extract in the same strength are to be expected since the former is an alum precipitate and relatively insoluble in water, while the latter is soluble in water and contains a fat solvent (thus making it more readily absorbed by the skin). In all probability, the patch test cannot be construed as an accurate index of the relative potency of these dissimilar types of extracts. However, the potency of the pyridine ivy extract is assured by the presence of positive reactions to patch testing with the material."

"The original plan of treatment for the prophylactic series included injections of the pyridine ivy extract of 0.1 ml., 0.2 ml., 0.4 ml., 0.8 ml. of the 1:50 dilution; then 0.4 ml., 0.7 ml., and 1.0 ml. of the 1:10 dilution given at five to seven day intervals. The 1.0 ml. doses were then repeated at monthly intervals. This schedule was followed without regard for the sensitivity of the individual as determined by the patch test.

"In 1945, 46 patients were treated with the previously outlined schedule. Fifteen of these had no recurrence of the poison ivy during 1945; 18 experienced mild poison ivy, but of definitely less severity than in previous years, while 13 were no better than in previous years. In other words, 72 per cent of the patients had definite benefit from the treatment, while 28 per cent were not helped.

"Nine of these patients had been treated in 1944 with the alcoholic ivy extract with no relief of symptoms. Five of these were greatly improved and 1 moderately improved in 1945, after treatment with the alum-pyridine ivy extract. The remaining 3 were not helped. It is interesting to note that the 6 patients who registered improvement with the pyridine ivy extract had been unable to tolerate injections of the alcoholic ivy extract in doses exceeding 0.05 ml. of the 1:50 dilution but were capable of receiving injections of the pyridine ivy extract in doses of from 0.5 ml. to 1.0 ml. of the 1:10 dilution.

"Four of the patients among the original 46 treated were unable to follow the outlined schedule. These developed systemic reactions when their injection dosage exceeded 0.5 ml. of the 1:10 dilution of the pyridine ivy extract. All of the patients had successful seasons. It may be noted that the top dose attained by the more sensitive of these patients was the equivalent of a dose of 0.05 ml. of the concentrated alcoholic ivy extract, a dosage rarely if ever used in treatment with this material.

"In 1946, 25 of the original 46 patients continued treatment with the pyridine ivy extract. This treatment was consummated by the administration of injections at monthly intervals. The dosage administered varied from 0.5 ml. of the 1:10 dilution to 0.5 ml. of the concentrated extract, depending upon the sensitivity of the individual. Twenty-three of these patients had excellent seasons, experiencing no poison ivy. One patient developed mild poison ivy which remained localized at the point of known contact and which subsided readily by the use of a patent remedy. The remaining patient had a severe case of poison ivy of no less intensity than before treatment.

"In 1947, 13 of the original 46 patients continued their treatment through a third year. The treatment plan was a continuation of the annual treatment with the injections given at monthly intervals. During the winter months, 7 of the patients skipped a month but were able to tolerate their top injection dosage after two month intervals with no apparent discomfort. This may indicate that bimonthly injections may eventually be successfully incorporated in the plan of treatment. Twelve of these patients had extremely successful seasons, none of whom experienced even mild poison ivy. The remaining patient had one moderate attack of ivy dermatitis which remained localized at the point of contact. Four were patch tested with the pyridine ivy extract in dilutions up to the 1:5. All of the tests were negative. These cases had, in 1945, reacted positively to patch tests in a 1:1,000 dilution of the same material.

"In 1946, an additional 36 cases were treated with the pyridine ivy extract. At this time, the plan of treatment was altered to include injections of 0.4 ml., then 0.8 ml. of the 1:50 dilution, then 0.2 ml., 0.6 ml., and 1.0 ml. of the 1:5 dilution, given at five to seven day intervals and followed by monthly injections of 1.0 ml. of the 1:5 dilution of the pyridine ivy extract. By this procedure, it was possible to attain a top dose of 1.0 ml. of the 1:5 dilution in five injections, while with the previous schedule, seven injections were required to attain 1.0 ml. of the 1:10 dilution. Thirty-five of these patients were able to tolerate this dosage schedule without experiencing either local or systemic reactions. The remaining patient developed a moderate degree of local reaction and a generally distributed pruritus without visible lesions, following the injection of 0.6 ml. of the 1:5 dilution. The patient was later comfortably stabilized on a dosage of 0.4 ml. of the same dilution.

"On this routine, 29 of the 36 patients had satisfactory seasons. Sixteen of the 29 were wholly free from poison ivy, while 13 experienced one or more mild attacks of definitely less severity than in previous years. The remaining 7 patients were not benefited by the treatment.

"In 1947, 29 of the 36 cases treated in 1946 continued their treatment through a second year. The plan of treatment again was of the annual variety with injections of the top dose being administered at monthly intervals. Eighteen of these patients had little or no poison ivy throughout the season. The 3 remaining patients were among the group who had not done well in 1946. All of them, however, felt they were enough improved from their original status to warrant continuation of their treatment.

"In 1947, an additional 31 new cases were treated. The plan of treatment was the same as had been employed in 1946, whereby a top dose of 1 ml. of a 1:5 dilution of the pyridine ivy extract was reached in five injections at weekly intervals, followed by monthly injections of the top dosage. All of the patients accepted the outlined schedule without experiencing either local or systemic reactions. Twenty-six of these patients had successful seasons. One half of these had no poison ivy, while the other half had one or more mild attacks of less severity than in previous years.

"None of the cases referred for acute poison ivy were placed on phylactic therapy. A colleague of the writer has been able to treat the acute problems more rapidly and effectively by local treatments. No oral therapy was attempted."

Aureomycin in the Treatment of Anthrax — GOLD, HERMAN — *American Journal of Medicine*, 8: 31 (January) 1950.

The author reports 2 cases of anthrax treated with aureomycin.

Case 1.—E. W., a white male 52 years of age weighing 167½ pounds, was seen on January 13, 1949, because of a small itchy "pimple" on the dorsal surface of the left wrist. "It was first noted two days previously. Examination revealed a very small red papule with no surrounding edema. There was no adenopathy or fever. Because of the patient's occupation as a carder in a mill which had been the source of many cases of anthrax, this diagnosis was entertained but a smear revealed only red blood cells. On the fourteenth the papule was flatter; the only complaint was intense local itching. On the fifteenth the papule appeared to be absorbing. The patient continued to work but on the night of the seventeenth his wrist began to swell and was painful on motion. There was itching and a burning sensation at the site of the lesion which when seen on the eighteenth was the size of a nickel. A ring of fine vesicles surrounded the edge of the blue-red papule. Edema of the dorsum of the hand and wrist with bright erythema of the skin was present. A small slightly tender lymph node was palpable in the left axilla. The temperature was normal. Clinically there was no question concerning the diagnosis of anthrax. This was confirmed by recovery of *Bacillus anthracis* on smear and culture. In vitro antibiotic sensitivity tests were run on this culture .... with the following results: (1) Aureomycin, very sensitive, growth inhibited by 0.25 μGm./cc.; (2) streptomycin, moderately sensitive, growth inhibited by 3 μGm./cc.; (3) penicillin, resistant, growth inhibited by 30 units/cc.

"The patient was treated in ambulatory fashion with aureomycin (duomycin), 750 mg. by mouth every four hours. One hour after the second dose (five hours after institution of therapy) a second smear and culture from the lesion was made without any change being noted.

"The next morning the patient reported to the office feeling well except for slight itching at the site of the lesion. However, the edema had increased considerably, extending dorsally from the metacarpal joints to the upper one third of the forearm. The skin was bright red and tender at the margin of the spreading edema. The lesion showed large bluish vesicles that oozed freely. Axillary adenopathy was unchanged. The temperature was 99 to 99.4° F. Smear and culture, taken 23 hours after aureomycin therapy was started, were still positive for anthrax. On the twentieth, 48 hours after antibiotic treatment was begun, the edema of the forearm had cleared and the dorsum of the hand was only slightly swollen and dusky red in color. The lesion had the characteristic appearance of an anthrax 'pustule.' Smear from the lesion showed a definite decrease in the number of bacilli with unmistakable signs of degeneration but the culture was still positive. On the twenty-first the lesion showed a central dry black eschar, 5 mm. wide with slight induration around it. The hand was normal except for some discoloration of the skin. There was no adenopathy. The last dose of 750 mg. of aureomycin was taken at 9 A.M., thereafter 500 mg. were ingested every four hours for three doses, when the interval was lengthened to six hours. On the twenty-second the patient felt fine except for some looseness of the bowels. The lesion was dry, flat and black. There was no edema or adenopathy. Smears and cultures were negative for anthrax bacilli. On the twenty-fourth the

eschar began to separate at one margin; otherwise, there was no change. Medication was stopped after total consumption of 19.75 Gm. of aureomycin in six days. The blood count, urinalysis and sedimentation rate were normal.

"The eschar had completely separated on the thirty-first when the patient returned to work. The period of disability was 14 days. The small, shallow, granulating ulcer healed in three weeks.

"Case 2.— Mrs. A. F., a white female 27 years of age weighing 95 pounds, was well until April 8, 1949, when she noted a small pimple on the right hand just above the thumb. She was a spinner in the mill where the first patient worked. The next day pain and tenderness developed in the right axilla, especially after motion, which prompted her to seek medical advice. Examination revealed a very small papule on the right hand without swelling or redness. The epitrochlear nodes were not palpable but a tender lymph node the size of a marble was outlined in the right axilla. The temperature was 98.6° F." Anthrax bacilli on smear and culture of the lesion were demonstrated. "Sensitivity tests on this culture were identical to those in case 1 except that the organism was inhibited by 5 units of penicillin.

"April 10, 1949, the pustule was the size of a split pea with an area of redness and edema around it the size of a 25 cent piece. There was local itching and burning. Two large tender lymph nodes were palpable in the axilla. The temperature was 99.2° F. Aureomycin, 750 mg. every four hours, was ordered. On April 11, 1949, the lesion was flat, black and dry but the dorsum of the hand was moderately swollen and bright red in color but not painful. One single node was outlined in the axilla which did not appear to be as painful. Marked nausea and occasional vomiting developed. Aureomycin dosage was reduced to 500 mg. every four hours. Smear of the lesion showed an occasional anthrax organism but the culture was positive. On April 12, 1949, there was increased edema of the hand but the erythema of the skin had lessened. The pustule was dry and the size of a dime. The axillary node was barely palpable. The temperature reached 100° F. and the blood count and urinalysis were normal. Intense nausea and repeated vomiting were very distressing.

"On April 13, 1949, the hand was only slightly swollen and the skin was faintly red. The papule was flat and dry; the axilla was normal. Aureomycin was not tolerated even when given as one capsule (250 mg.) every six hours. Medication was stopped after 11.25 Gm. were ingested (some was lost through vomiting). April 15, 1949, the patient was symptom free and her hand was normal in contour. The eschar began to separate on the eighteenth and came off a week later. The patient returned to work on April 25, 1949. The ulcer gradually filled with clean granulation tissue and healed in two weeks."

"Clinically these patients responded as rapidly or perhaps a little faster than patients previously treated by the author with large doses of penicillin.

"Like other therapeutic agents aureomycin did not seem to affect the course of development of the anthrax pustule."

"The advantages of oral medication, ease of administration, lack of sensitizing reactions and benefits to be derived from the fact that this therapy allows for ambulatory management need no further elaboration."

Prognosis After Nephrectomy for Renal Tuberculosis—OPPENHEIMER, GORDON D. AND NARINS, LESTER — *Journal of Urology*, 62: 804 (December) 1949.

"The present study concerns itself with 117 patients with renal tuberculosis admitted to the ward service of the Mount Sinai Hospital from 1928 through 1945. Of these 117 patients, 106 were nephrectomized for unilateral renal tuberculosis, and 11 were not treated surgically either because of presence of demonstrable bilateral renal tuberculosis, or active extrarenal infection. Twenty-nine of the patients had complete ureteronephrectomy performed according to the technique of Beer, and in the others, simple nephrectomy with removal of as much ureter as possible was done. The indications for ureteronephrectomy were tuberculous ureteral involvement with stenosis and dilatation. Of the 106 surgically treated cases, 2 died postoperatively and 8 were immediately lost

to follow-up, leaving 96 cases that have been followed. Of the 117 cases, 71 occurred in males, and 46 in females." The ages varied from 10 to 70. "There were concomitant active pulmonary lesions in 15 cases, and genital or bone lesions in 15 cases preoperatively."

Fifteen of the operative cases developed genital or osseous tuberculosis, and 17 cases developed contralateral renal involvement. "There were also 17 cases of residual tuberculous cystitis. The average length of survival of the patients who developed genital or osseous tuberculosis postoperatively was 7.3 years; of those who developed contralateral involvement, 6.2 years, and of those who had residual tuberculous cystitis, 8.6 years.

"During this period there were 11 instances of adnexal tuberculosis in the male in which no upper urinary tract lesions could be demonstrated. The age variation was between 24 and 79 years. The lesion in the 10 cases was unilateral epididymitis, and in 1 case bilateral epididymo-orchitis. Four patients had epididymectomy performed, 6 had epididymo-orchidectomy done and 1 was not operated upon. In all the operative cases, the diagnosis was confirmed by the pathological laboratory. The length of survival (and/or follow-up) varied from 1-15 years with an average of 6.4 years. In no case was there a development of gross upper urinary tract tuberculosis. One patient subsequently had a nephrectomy for a nontuberculous calculous pyonephrosis. Two cases had associated pulmonary tuberculosis. Of these, 1 survived 4 years, dying of pulmonary tuberculosis, and 1 patient is living 15 years after epididymo-orchidectomy, with an arrested pulmonary lesion."

Nephrectomy for unilateral renal tuberculosis affords the patient a better than even chance for a 5-10 year survival. "Even including the number of cases lost to follow-up, the survival rate for a 5-10 year period is 55 patients alive of 96. . . . An appreciable number of patients have survived more than 15 years and are ostensibly cured. For the present time, nephrectomy for unilateral renal tuberculosis has proved to be a time-tested and efficacious method of treatment. Until a long-followed series of cases treated solely with streptomycin can be shown to compare favorably with surgically treated cases, nephrectomy for unilateral renal tuberculosis, perforce, must be regarded as a reliable method of treatment."

Pediatrics

Jaundice and Anaemia in the Newborn — MacCarthy, Dermod — *Practitioner*, 164: 19 (January) 1950.

"The best approach to the clinical problems of jaundice in the newborn infant is by a preliminary study of the physiology of pigment metabolism and the blood changes that take place at and after birth. A knowledge of the rather complex changes that result in physiological jaundice simplifies the understanding of other forms of jaundice and helps in making decisions at the bedside of the sick infant."

It will perhaps simplify discussion of the clinical types of jaundice if the most important data are enumerated and arranged in a logical order.

"1. The total number of red blood corpuscles at birth is in excess of the number required for extrauterine life.

"2. The total number of red cells in circulation after birth is influenced by whether the umbilical cord is tied early or late. If late, the infant receives a considerable volume of blood from the placenta; if early, this 'placental transfusion' is prevented from reaching the child. Physiological jaundice is more frequent in infants in whom the cord has been tied late and who therefore start life with a larger excess of red cells than those who have had the cord tied early."

"3. There is hyperbilirubinaemia of the cord blood or neonatal blood of the majority of infants.

"4. The plasma gives the indirect positive van den Bergh reaction indicating that the pigment has not passed through the liver cells and the jaundice is not obstructive.

"5. The source of the excess of bilirubin in foetal life is thought to be areas of breakdown of maternal blood in the placenta.

"6. Destruction of red cells which begins a few hours after birth further increases the amount of bilirubin in circulation."

7. An increased rate of destruction of erythrocytes in the neonatal period, which has long been conjectured but has always been a difficult matter to prove satisfactorily, was demonstrated recently. Taking placental blood as representative of the newborn infant's blood, placental erythrocytes were injected into other newborn infants and the length of their survival measured. As a control the erythrocytes of a normal adult were injected into other infants and their survival estimated. During the first 10 days of life the placental erythrocytes (and therefore, one may assume, the erythrocytes of the normal newborn infant) were destroyed at about twice the rate of the adult cells; thereafter the rate was the same in both. "Because of the relatively greater number of erythrocytes in the blood of the infant the amount of bilirubin produced is probably three times greater proportionally than that normally being produced by the adult. Adults are able to deal with an even greater output of bilirubin than this without becoming jaundiced: not so the newborn infant; an impairment of the liver function in excreting bilirubin may therefore be inferred.

"8. Excretion of bile pigment by the liver in foetal life is shown by the presence of the pigment in the meconium, but evidently only part of the circulating bilirubin is dealt with in this way, for in cases of congenital obliteration of the bile ducts, although the meconium may be lacking in pigment, jaundice is not present at birth.

"9. The placenta probably eliminates the bulk of surplus pigment from the foetal circulation."

"10. The higher the level of serum bilirubin in the cord blood the greater the frequency, severity and duration of physiological jaundice.

"11. The total excretion of bile pigments in the stools in the first five days of life is less in the icteric than in the nonicteric infant. The urinary excretion of urobilin (which depends first upon the excretion of bilirubin by the liver into the bowel and then reabsorption into the blood stream of the oxidized pigment from the bowel) is also less in the icteric than in the nonicteric infant. The greater the bile pigment content of the meconium of

the newborn the less the tendency to develop jaundice. These observations strongly suggest an impairment of hepatic excretion of bilirubin in those infants who become jaundiced.

"12. The excretion of bromsulphthalein by the liver (as estimated by its elimination from the blood stream) has been found to be retarded in the first 10 days of life, but other tests of liver function in the newborn have proved remarkably normal. There is no correlation between the height of the bilirubinaemia and the delay in bromsulphthalein excretion; the evidence afforded by this test is therefore only suggestive. The one test required to complete the picture, the actual measurement of bilirubin excretion, still presents great difficulties of performance.

"13. The premature (immature) infant, as might be expected if the theory of liver function impairments is correct, shows a greater frequency and a longer duration of jaundice than the full term infant.

"14. Identical twins (who may be presumed to have a similar physiological constitution) behave alike as to the development or nondevelopment of jaundice; whereas nonidentical twins often differ.

"Clinical Aspects of Jaundice in the Newborn.—Physiological jaundice should be regarded as the outward manifestation in certain babies of a hyperbilirubinaemia present to some degree in all. . . . The important points for the clinician to note are that it seldom appears before the second day of life, that if it deepens its progress is measurable from day to day rather than from hour to hour (as in icterus gravis), and that it is usually gone by the tenth day, although in premature infants, and very exceptionally in full term infants, it may last up to four weeks.

"Icterus Gravis.—In icterus gravis (haemolytic disease of the newborn, erythroblastosis foetalis) the same physiological conditions prevail, but the haemolytic process instead of beginning after birth is active during foetal life and is much more intense. There is also an anaemia resulting from the haemolysis, and this factor may be of much more importance than the jaundice."

"Icterus gravis is a clinical picture which is often thought to be, and indeed appears to be, in some way precipitated by the change to extrauterine life. . . . The explanation of the jaundice here is the same as in physiological jaundice; but the quantity of bilirubin liberated is very much greater and, the imperfection of liver function being the same as in any other infant, the jaundice appears much sooner and deepens rapidly. The jaundice and progressive anaemia after birth are the clinical signs of a process that has already been going on for some time before birth. In severe cases, of course, the compensatory erythropoiesis and placental excretion of bilirubin are inadequate, the foetus is jaundiced and the pigment may colour the membranes and the liquor. The anaemia is intense, heart failure ensues with dropsy and death in utero or at birth (hydrops foetalis). The severe cases which survive for a few hours after birth often show cyanosis, ecchymoses, flaccidity, and failure of all the normal reflexes.

"Diagnosis: When jaundice is present at birth it may be assumed to be due to haemolytic disease. Congenital syphilis affecting the liver and congenital atresia of the bile ducts, although giving rise to jaundice soon after birth, do not do so in intrauterine life. . . . The rapidly deepening jaundice of haemolytic disease will make the diagnosis certain in a few hours.

"When a baby is normal at birth but becomes jaundiced within 24 hours the diagnosis may be less certain. The features which point to haemolytic disease are as follows:

"1. A history of the mother having received a blood transfusion, even remotely in her past. In such a case the first-born child may be affected.

"2. A history of one or more previous pregnancies or miscarriages.

"3. A history of jaundice at birth or a known case of haemolytic disease in other children of the family.

"4. The placenta may have been noticed to be abnormally large. Also the cord jelly, even in mild cases, may have shown some yellow staining at birth.

"5. The spleen is palpable. It should be felt with the fingers of the right hand approaching from the baby's right side. Likewise the liver, approaching with the left hand from the baby's left side, may be felt to be enlarged but less constantly than the spleen.

"6. The infant may show pallor as well as jaundice and is usually very lethargic. Both jaundice and pallor increase at a rate that may be appreciated in hours rather than days.

"7. Erythroblastaemia. Although in mild cases the number of nucleated red cells may fall within the normal range (1 to 15 per 100 white cells on the first day of life) there are usually many more than this and examination of a stained blood film may reveal that they far outnumber the white cells and that there are many primitive forms.

"8. Anaemia. The evaluation of a haemoglobin reading on capillary blood taken a few hours after birth needs caution. The importance of the 'placental transfusion' comes in here. If the cord was tied late, the infant who was anaemic at the time of birth may have received an extra amount of blood sufficient to put its haemoglobin temporarily within the normal range (15 to 22 Gm. per cent). If the reading is below the normal range it is certain that anaemia exists.

"Special Tests: In laboratories equipped with the special serums the diagnosis may be confirmed by demonstrating the presence of the Rh antibody in the infant's blood. The antibody is fixed to the surface of the red blood cells. The ingenuity of the test lies in the fact that it is not the Rh antibody itself that is detected but the globulin with which it is compounded. The test, which is performed by mixing the infant's cells with rabbit's serum sensitized to human globulin, is known as the antihuman globulin test or the Coombs test.

"Rh typing reveals that the mother is Rh negative and the infant Rh positive. Very rarely differences between the AB groups of mother and child may give rise to sensitization of the mother and production of haemolytic antibodies.

"Subsequent Course of the Disease: If untreated, the baby becomes progressively more and more anaemic. The jaundice deepens, but this is of less importance than the anaemia, which is likely to prove fatal. Three grave complications may arise during the first week:

"1. A haemorrhagic tendency develops, associated with hypoprothrombinaemia (a result, probably, of deficient synthesis of prothrombin by the liver), and epistaxis or repeated haematemesis or haemorrhage into the lungs may be the final cause of death. This picture should not be confused with haemorrhagic disease of the newborn, in which spontaneous bleeding (notably melaena) occurs in the first week of life. This has no connexion with jaundice although physiological jaundice may be present at the time.

"2. Kernicterus (bile staining of the basal ganglions). Fairly constantly about the third or fourth day an infant with this complication shows signs first of cerebral irritation, then profound cerebral depression. The features usually observed are: a plaintive grunting cry, convulsions, twitching, head retraction, spasticity and spontaneous gyratory movements of the arms. Within 24 hours or less there follows loss of sucking and swallowing reflexes, respiratory arrhythmia, gasping, apnoea and death. Cases with milder symptoms may recover.

"The clinical picture of cerebral damage associated with deep jaundice in the newborn seems to be peculiar to icterus gravis. It does not occur with the jaundice of biliary obstruction, and it is now agreed that the damage to the nerve tissue of the nuclei of the brain and medulla takes place independently of the presence of bile pigment, the staining of the nuclei being a secondary change in already damaged tissue. Nuclear jaundice has been demonstrated post mortem in infants dying of severe sepsis, who in life showed jaundice and cerebral disturbances."

"A few cases of icterus gravis develop, in later infancy, spasticity and choreoathetosis. These infants are usually grossly mentally deficient. In some there will be a history of a 'cerebral' episode in the first few days of life; in others these symptoms will have escaped notice. There is no evidence that icterus gravis, or Rh immunization per se, can cause mental defect, except indirectly as a result of the neurological changes of kernicterus. Infants who recover without these sequelae develop normally."

"3. In severe cases a toxic liver damage is a demonstrable pathological change. The deepening lethargy of these infants is reminiscent of the cholaemia of acute yellow atrophy of the liver and, as a clin-

ical description, 'liver failure' is apt for those cases of icterus gravis which die without signs of kernicterus, heart failure, haemorrhage or severe anaemia."

Treatment: When the maternal history and laboratory data make it probable or certain that the child will be affected, the umbilical cord should be clamped at the moment of birth. "This prevents the infant from receiving an extra quantity of blood (the 'placental transfusion') containing antibody and cells destined to be destroyed; blood that the infant would be better without. Next, 10 ml. of blood should be taken from the umbilical vein with a syringe and put into an oxalate bottle. This may be used for the Coombs test, Rh typing, the haematocrit, and an accurate estimation of the haemoglobin. On the information given by these tests the diagnosis and the need for transfusion, and the urgency thereof, can be settled."

When the diagnosis is made after birth, it must be remembered that very mild cases may not require any treatment at all. "Mild or moderate cases are certain to become anaemic, but the main question to be decided here is the urgency or otherwise of transfusing. Any sign of haemorrhage, of course, increases the urgency. Infants who are noticeably anaemic at birth should be transfused at once. Haemoglobin estimations will give a rough guide as to the rate at which the anaemia is progressing. A level of 80 per cent on the first day of life indicates that the infant is severely affected.

"Breast Feeding. Antibody can be detected in the mother's milk, but apparently the amount absorbed, if any, is negligible and no immediate harm results."

Induction of Labour. "In certain severe cases which have been delivered at the thirty-fifth week of pregnancy and survived, it is difficult to believe that the baby would have been born alive had it remained in utero for another five weeks. One of the objections raised against early induction is that to the dangers of haemolytic disease is added the risk of prematurity. Most of these babies, however, at the thirty-fifth week have quite reasonable birth weights, not less than 4 1/2 pounds, and do not present any difficulty as 'premature babies.' This may be because the obstetrical complications that usually form the background of prematurity are not present here. Still earlier induction would therefore seem to hold out more hope when a severely affected case is anticipated; but unfortunately the earlier in pregnancy that induction is attempted the less often does it succeed. It must also be remembered that the state of the foetus is partly determined by the balance between the haemolytic process to which its blood is being subjected, and by its own powers of blood regeneration. Severe cases are fighting a losing battle throughout and will probably be found in a critical state however early they are rescued from intrauterine conditions.

"Obstructive Jaundice. — Generally speaking the clinical diagnosis of obstructive jaundice in the first four weeks of life is made on the appearance of the stools, which are white and pasty, and the colour of the urine, which contains bile pigment, rather than on the character or time of appearance of the jaundice itself. When obstruction is complete at birth the meconium may be pale."

The possibility of obstructive jaundice being present at birth is difficult to reconcile with one's knowledge of foetal physiology. "At all events the onset is early and the colour deepens steadily to a greenish hue. In spite of this there is astonishingly little disturbance of feeding and nutrition and the child may thrive for many weeks. The liver is usually palpable about 1 fingerbreadth, but marked enlargement associated also with enlargement of the spleen suggests cirrhotic changes, and if wasting and ascites are added this is certain.

"Such a clinical picture is straightforward enough, but there are cases in which the jaundice appears late and cases in which physiological or haemolytic jaundice is present at first but signs of biliary obstruction supervene later. The older physicians spoke of 'icterus neonatorum gravis (seu prolongatus).' In both instances the obstructive features may be transient, lasting a few days or weeks, and the obstructive phase may recur several times."

"Main Causes of Obstructive Jaundice: (1) Congenital anomalies of the bile ducts. (2) Cystic dilatation of the bile duct. Seldom seen in the first month. Abdominal swelling nearly always palpable. (3) Inspissated bile plugging main ducts or com-

mon duct. (4) Conversion of bile ducts into a fibrous cord. (5) Pigment stones. (6) Intrahepatic biliary obstruction due to liver-cell damage which may lead to cirrhosis. There is much evidence to suggest that the last four may be associated with haemolytic disease.

"Preliminary investigation must include Rh typing and tests for Rh antibody in mother and infant, a blood count and examination for erythroblastaemia, and the Wassermann reaction. In view of the very bad prognosis of unrelieved obstructive jaundice nearly all cases of persistent obstruction deserve a laparotomy. The postoperative mortality is high when clinical deterioration has set in, but a preliminary transfusion or paracentesis when either anaemia or ascites is present may bring about a marked improvement.

"Other Rare Forms of Neonatal Jaundice.—Congenital Syphilis: The liver is much enlarged. Jaundice is slight. Other features of congenital syphilis are present and the Wassermann reaction is positive.

"Severe Septic Infection: The infant having been well for the first week of life becomes very ill on the fifth day or later. Infection of the umbilicus may sometimes be obvious. There may be pyrexia, diarrhoea, vomiting and marked anaemia. Haemolytic disease can only be excluded with certainty by Rh typing and the Coombs test.

"Familial Acholuric Jaundice: Persistent mild jaundice, slight anaemia and splenomegaly are occasionally seen in the newborn infants of affected families. Precise diagnosis rests on the detection of spherocytosis and increased corpuscular fragility and the exclusion of Rh or blood group isoimmunization."

Anaemia in the Newborn.—"The number of erythrocytes in the blood a few hours after birth varies from 5.5 to 7.5 millions and the haemoglobin is in the region of 140 per cent. There is a steady fall in the haemoglobin level and red cell count during the first three months of life, the haemoglobin reaching a level of about 75 per cent. This is due to the combined effect of diminished blood formation and rapid growth, with accompanying rapid increase in blood volume, and is a normal physiological picture and not a state of anaemia. The effect is particularly marked in the premature infant, who starts life with a slightly lower red cell count than the full term infant and whose rate of increase in size is relatively much faster. Babies of 3 pounds or less often have a haemoglobin level of 50 per cent or less when 10 weeks old. Blood transfusion can have only a temporary effect, and so long as the infant is thriving need not be considered. Iron given in the early weeks to premature babies does nothing to prevent the fall in haemoglobin, but when blood cell production increases spontaneously at about the third month the rise of haemoglobin is slightly more rapid in babies who have had iron from the start than in those who have not. This small benefit seems to be worth having. A good way of giving iron to premature infants is in the form of iron and ammonium citrate. One grain (65 mg.) will dissolve in 3 minims (0.2 ml.) of water. The first dose at the age of 3 weeks should be one drop three times a day, in the feed, and should be increased slowly to nine drops three times a day, a total of 9 grains (0.6 Gm.) per day.

"Pallor: There is always a change from the rather plethoric appearance of the newly born infant on the first day to a paler, somewhat shrunken appearance on the third day, but the mucous membranes remain a good colour. The sudden appearance of intense pallor which also affects the mucous membranes is due to haemorrhage. If the source is not visible (umbilical cord, umbilicus, haematemesis) bleeding into the bowel must be remembered. Transfusion is urgent. Group O, Rh-negative blood should be used. The blood volume is calculated roughly at 40 ml. per pound (0.45 Kg.) of body weight and one third or half this amount will probably need to be restored.

"Intense pallor of insidious onset is seen in congenital anaemia, another form of haemolytic disease of the newborn in which jaundice is inconspicuous or absent and haemolysis more gradual. At the age of 3 weeks or later the infant appears quite blanched and is generally oedematous.

"Acute infection of any kind in the newborn may be accompanied by a moderate degree of anaemia and the correction of this by transfusion may speed recovery."

Streptomycin in Miliary Tuberculosis and Tuberculous Meningitis — LICHTENSTEIN, A. — *Acta paediatrica*, Supp. 75, p. 5, 1949.

Streptomycin can save cases of miliary tuberculosis and tuberculous meningitis. On the other hand, only a small percentage, particularly of the meningitis cases, are restored to complete or almost complete health. "The great majority either die or are not completely cured." The author emphasizes the fact that a number pass into a chronic or subchronic state. "The streptomycin produces, in fact, a disease picture previously scarcely observed, a subchronic tuberculous meningitis with cachexia, paralyses, convulsions and often partial or total block with hydrocephalus and marked psychical deterioration.

"In judging the value of streptomycin in tuberculosis one must bear in mind that the effect of this substance on the tuberculosis bacillus is mainly a bacteriostatic one and only to a small extent a bactericidal one, at any rate in the concentrations which occur in the fluids or organs of the body (with the possible exception of the kidneys)." In 1 of the author's cases the presence of tubercle bacilli in the liquor and fresh miliary tubercles in the meninges could be established in connection with an operation for ventile-hydrocephalus undertaken 11 months after the onset of the disease, when the patient had received c. 300 Gm. of streptomycin.

"Certain experimental investigations indicate, however, that the effect of streptomycin on living subjects is not merely a function of the concentration. There may also be some kind of indirect effect."

"A number of other factors concerning streptomycin also remain obscure. These include its resorption, distribution and excretion. The concentration in the cerebrospinal fluid is of particular interest." Apparently it varies widely; in the author's cases it varied between 1 and 8 units per cc. during periods of intramuscular injection only, although it was usually only 1 to 2 or below—i.e., a lower concentration than is ordinarily required for retarding the growth in vitro. "Yet it should be pointed out that a number of meningitis cases have been saved by intramuscular treatment only."

"Where dosage is concerned, two considerations must be kept in mind; the toxic effect of the streptomycin, particularly on the vestibular nuclei, and the risk of inducing resistance." The toxicity forces one to keep the dosage down, but small doses probably increase the danger of inducing resistance. "The extent to which the tuberculosis bacillus in the living body becomes resistant is still not known. Resistance comes into existence easily in vitro however."

At present the author's dosage is 100 mg. four to six times daily intramuscularly and 25 to 50 mg. intrathecally, at first once a day but later every other or every third day over three week periods for at least four to five months. The author attempts, however, to reduce both the amount of the individual doses and the number of injections per day. "If it should appear that maintenance of a constant streptomycin concentration in the blood and body fluids is not necessary, it might be possible to reduce the doses considerably and thereby also the danger of harmful secondary effects.

"Treatment of tuberculous meningitis must, finally, always present the difficulty that because of poor vascularization of the brain substance, any intracerebral foci are very difficult for therapeutic agents to reach. It is then an open question whether treatment of the primary infection, by means of which one might be able to prevent meningitis, would not be preferable." Undoubtedly this would be right if one had access to an effective and a toxic substance. "Streptomycin is so toxic, however, that it very often causes irrevocable vestibular injuries." These may follow after only a few grams—in one of the author's cases after only 6 1/2 Gm.—although they are much more common after larger doses. "Injuries to the cochlear nuclei with resultant partial deafness also occur, if more rarely." The toxicity of streptomycin is such that the author does not consider it suitable for treatment of ordinary primary tuberculosis, benign as it usually is.

Streptomycin has marked the beginning of a new era in the history of the treatment of tuberculosis. For the first time one has a substance at hand with which one may be able to save a number of

cases of formerly almost hopeless types of disease. "But the effect is still often too weak and uncertain. In many respects streptomycin treatment of tuberculosis is still in an experimental stage. Last but not least, the substance is not atoxic."

The Electroencephalogram in Cases of Tuberculous Meningitis — LICHTENSTEIN, A. AND MELIN, K.-A. — *Acta paediatrica*, Supp. 75, p. 75, 1949.

"Formerly the prognosis in cases of tuberculous meningitis was almost hopeless. Nowadays, thanks to streptomycin, treatment is often more successful. Yet many cases still defy treatment, ending either in death or in recovery with more or less serious defects."

"Some cases run a malignant course from the beginning in spite of intensive treatment. Others show themselves somewhat responsive to treatment, but pass into a subchronic stage characterized by hydrocephalus, pareses, convulsions, and deterioration of the intellect. Still others respond to treatment well in the beginning but later suffer relapse. Finally, in certain cases treatment gives excellent results; i.e., complete or virtually complete restoration to physical and psychical health."

The authors attempt to determine the prognosis and individualize treatment by utilizing all available control methods. "The cerebrospinal fluid is examined directly for tubercle bacilli and used in cultures and guinea pig tests. The cell content and albumin content of the C.S.F. are determined continuously, as well as the lumbar sugar-blood sugar quotient. The gold sol reaction also seems to be of value, as are the streptomycin concentration in the blood and the lumbar fluid. Continuous checking of the eyegrounds for chorioidal tubercles and papillary stasis are also important in ascertaining the course of the disease, and frequent checkings of vestibular and cochlear function are a matter of routine.

"Yet in spite of all these examinations it is often very difficult to determine the prognosis in any one case. Therefore information concerning the actual condition of the cerebral cortex is of great value." The authors have felt it of interest to follow their cases of tuberculous meningitis electroencephalographically, particularly in view of the possibility of thus obtaining further aid in the determination of the prognosis.

In the beginning some doubt was cast on this possibility by the investigations into the influence of antibiotics on the central nervous system. "By means of experiments on animals these investigators showed that penicillin, streptomycin, streptothricin, and other antibiotics have a distinct effect on the EEG."

The authors examined first 2 children aged 2 months and 8 months. "They were treated with streptomycin for miliary pulmonary tuberculosis without meningitis or other signs of cerebral affection. At the time of the examination the streptomycin concentration in these children's blood varied between 5 W.E. and 15 W.E. The electroencephalograms recorded showed no pathological changes. Thus no electroencephalographically recordable cerebral effects could be demonstrated in these patients, who upon being treated with streptomycin showed ordinary concentrations in the blood."

Under these circumstances it seemed possible that electroencephalographic control of the authors' tuberculous meningitis cases might give valuable results.

All the authors' examinations were made at the electroencephalographic laboratory at Kronprinsessan Lovisa's Children's Hospital with a Grass electroencephalograph, Model III. "Silver disk electrodes stuck to the scalp with collodion were used. Between the electrodes and the scalp there was a thin layer of electrode jelly. A total of 10 electrodes were applied in each examination; namely, frontally, parietally, temporally, and occipitally on both sides, in addition to which the ear lobes were used as 'indifferent' electrodes. Both unipolar and bipolar recordings were made from all the electrodes.

"Thus far 7 children aged 1 1/2 to 11 years have been examined. All have had bacteriologically verified tuberculous meningitis and have undergone streptomycin treatment. All 4 cases which were examined early in the course of the disease then showed pathological changes on the electroencephalogram.

"After completed streptomycin treatment 2 of the children, a 6 year old boy

and a 3 year old boy, were clinically completely cured. After clinical recovery they were again examined electroencephalographically, in the first case 5 and 10 months after the onset of the disease and in the second 7 and 15 months afterwards. The EEGs of both children were interpreted as normal, although somewhat generally slow in the case of the 6 year old.

"The first EEG examination, c. 3 1/2 months after the onset of the disease, of a 2 year old girl who showed considerable clinical improvement during treatment revealed bursts of large 5/sec. waves on the record. Shortly after this phenomenon was observed there was clinical deterioration, and a second EEG examination c. 2 1/2 months later showed marked pathological changes. Approximately 1 month thereafter the child died and autopsy revealed an abundance of tubercles in the gray matter of the brain. In this case the EEG was the first examination method to indicate that the disease was becoming worse.

"An 11 year old boy was examined only once, c. 4 months after the onset of meningitis. Bursts of enlarged 4/sec. waves were noted on the record. This patient, who died 4 months later, also proved to have an abundance of tubercles in the gray matter.

"In the other 3 cases EEG examinations were carried out repeatedly. A 1 1/2 year old girl and a 4 1/2 year old boy both showed considerable clinical improvement. At the first EEG examination 11 days and 3 days, respectively, after the onset of the disease, both showed a generally and pronouncedly pathological EEG with many large, slow waves. The EEG in both gradually became normal, and at the present time, 12 and 7 months, respectively, after the onset of the disease, is fully normal. It is noteworthy that this normalization process took place in the course of intensive intramuscular and intrathecal streptomycin treatment." This lends further support to the authors' assumption that the EEG changes produced by antibiotics in experiments do not arise in clinical treatment, at any rate not to such an extent that they are able to affect appraisement of the actual condition.

"In the seventh case, a 2 1/2 year old girl, the first EEG examination was made three months after meningitis was established. At the time her clinical condition was good and the record was entirely normal. This was still the case when she was examined a month later. About three weeks thereafter clinical symptoms of deterioration appeared, with a rise in temperature, bad humour, general indisposition, and vomiting. The lumbar fluid showed an increase in the number of cells, increasing albumin content, and somewhat less lumbar sugar than before. At the same time repeated EEG examinations revealed bursts of large 5/sec. waves.

"Of the 7 patients examined at Kronprinsessan Lovisa's Children's Hospital, 4 have recovered or shown considerable clinical improvement thus far. All of these have also had a normal EEG. Of the other 3 patients, 2 have died and 1 has shown symptoms of clinical deterioration. As their conditions have deteriorated the electroencephalograms of these 3 have shown bursts of 4-5/sec. waves of high amplitude. In 1 of the cases such EEG findings constituted the first indication that the patient was becoming worse. Thus to judge by these investigations, repeated EEG checkings throughout streptomycin treatment of tuberculous meningitis definitely help the examiner to follow the course of the disease. The EEG may even provide the first observable indication of deterioration and thus be of prognostic value. If the EEG becomes more pathological in the course of treatment, it may also indicate the desirability of intensifying the treatment."

Purpuric Manifestations Occurring in Measles in Childhood — MILLS, STEPHEN D. — *Journal of Pediatrics*, 36: 35 (January) 1950.

Personal experiences with a child exhibiting purpuric manifestations following measles is reported. "This is not to be confused with the type of measles which is characterized by a hemorrhagic initial rash and usually terminates fatally.

"Case Report.—A 6 year old boy whose condition had been followed from birth and who gave no history of previous bleeding tendencies was seen with a fever of 103° F. and Koplik's spots in the buccal mucosa. Beyond injection of the conjunctivas, the physical examination did not

reveal any abnormality at this time. He was given 4 cc. of gamma globulin intramuscularly, and also aspirin for the fever. A typical measles rash appeared two days later. He was not unusually ill with measles and was not seen until a week after the first visit, at which time the rash was fading and he had a mild cough with nasal congestion.

"Ten days after the onset of the disease he complained of bleeding from his mouth. He had had no fever for three days and had been up and about the house. At this time there were petechial hemorrhages on his legs and trunk. There were two small excrescences of the buccal mucous membrane opposite the last molar teeth which bled on pressure. The liver, spleen, and lymph nodes were not enlarged. The boy did not feel ill. The erythrocyte and leukocyte counts of the circulating blood were normal. The platelet count was 37,300 per cu.mm. and the bleeding time was 70 minutes. Determination of the clot retraction time was not done.

"Two days later he had severe epistaxis which was uncontrollable by the use of nasal packs, and he was hospitalized. The nasal hemorrhage temporarily stopped after insertion of an epinephrine pack. He was given 250 cc. of whole blood by transfusion. He continued to bleed from the nose, and cauterization of the vessels of the nasal septum was done on two occasions. Blood in the amount of 250 cc. was given six times at almost daily intervals. Petechiae continued to appear on the skin, tongue, and oral mucous membrane. There was no enlargement of the liver, spleen, or lymph nodes. The blood showed a moderate secondary anemia and leukocytosis with normal differential counts and continuously low platelet counts that ranged from 20,000 to 40,000 per cu. mm. The boy was dismissed from the hospital improved, on the fifteenth day after admission. There were no further hemorrhages of the skin or mucous membrane but his platelet count was still 37,500.

"Two weeks after dismissal from the hospital the platelets numbered 90,000 and three months later they had risen to 140,000. There was no recurrence of bleeding and the erythrocyte, leukocyte, and differential counts were normal. The boy improved steadily and made a complete recovery in every way.

"A review of the records from the files of the Mayo Clinic in the pediatric age group for the past 30 years revealed 10 instances of purpura following measles. No case was considered in which the purpura did not develop within a month of the onset of the measles rash. Six patients showed the bleeding tendency within two weeks of the onset of the measles exanthem.

"The patients were evenly distributed as to sex. The ages varied from 11 months to 8 ½ years. Two patients gave a history of repeated nosebleeds.

"The bleeding was into the skin and mucous membranes in 6 cases and into the skin alone in 4. Epistaxis was reported in one-half the cases. Hemorrhage from the bowel occurred twice, and from the urinary tract, once. Enlargement of the liver, spleen, and lymph nodes was recorded in 2 cases. Blood studies showed a mild to moderate degree of secondary anemia.

"The number of blood platelets was reduced below 90,000 in 4 cases, with prolongation of the bleeding time beyond 15 minutes. Clot retraction was delayed beyond two hours in 3 of the 4 cases in which the test was done. The diagnosis of thrombocytopenic purpura was made and splenectomy was carried out in 3 of the 4 cases. Splenectomy was deferred in the fourth case as the symptoms seemed milder than in the other cases.

"Recovery of all but 2 patients took place. One of these was a 21 month old female infant with a history of fever, petechial hemorrhages of the skin, and melena eight days after the onset of the measles rash; she died the day following admission to the hospital despite three blood transfusions. Necropsy disclosed a bleeding Meckel's diverticulum as well as hemorrhages throughout the bowel and stomach. The liver and spleen were normal in size, and the platelet count and the bleeding time were normal. Clot retractility was not recorded. A diagnosis of toxic purpura was made in this instance.

"The second death occurred in the case of a 9 year old boy one month after dismissal from the hospital. He had purpura involving his lower extremities. His platelets numbered 36,000 and the blood smear

showed evidence of acute leukemia. One other patient had evidence of leukemia in the blood smears but he could not be followed up after his return home.

"After elimination of the 4 patients with thrombocytopenic purpura and 2 with leukemia in whose course the occurrence of measles might be considered incidental, there remained 4 patients who could reasonably be considered to have had purpura following measles. All of these recovered except the infant with the Meckel's diverticulum and intestinal hemorrhages. No treatment was given to any of these patients except the transfusion of blood performed in the case of the child who died. In the other 3 patients the purpura was mild and lasted but a few days. It involved only the skin and not the mucous membranes. There was no enlargement of the liver, spleen, or lymph nodes reported, nor were the blood platelet counts or bleeding time abnormal. Estimations of clot retractility were not done in any of these patients. It would seem that in a case of uncomplicated measles, the appearance of purpura need not be a serious prognostic sign. As all but 3 of the previous 10 cases were encountered prior to the advent of sulfonamide therapy, these drugs were not a factor in the production of the purpura. Though amidopyrine has been incriminated in causing damage to the hemopoietic system as evidenced by purpura, there was no record of its use by any of the patients whose records were reviewed."

"The outlook for the ultimate recovery of patients who exhibit purpuric manifestations following measles is good. However, one must be certain that such purpura is not an evidence of a blood dyscrasia or the accompaniment of a severe infection."

Peptic Ulcer in Children, with Particular Consideration of Its Frequency—KARLSTRÖM, FRITZ—*Helvetica paediatrica acta*, 4: 455 (December) 1949.

Two forms of peptic ulcer must be distinguished in childhood; namely, one occurring almost exclusively in infants and one involving chiefly older children, above the age of 10. The peptic ulcer of infants is usually secondary; as primary diseases acute and chronic infections, like septicemia, erysipelas, tuberculosis and syphilis, endogenous intoxications like nephritis with uremia, circulatory disturbances, eczema, and traumas must be taken into consideration, and an ulcer will appear the more readily the more cachectic the infant. There may be alarming symptoms like hematemesis, melena or perforative peritonitis, or the symptoms may be insignificant making clinical diagnosis difficult. The affection may be observed in debility. After infancy the incidence of peptic ulcer decreases probably due to a decrease of the incidence of the causal affections. However, primary peptic ulcer may be found in young children and occasionally even in infants. Peptic ulcer of older children is considered rare, but the actual incidence is probably higher as the diagnosis is not always made. However, the incidence is certainly small compared to that in adults; several large clinics reported an incidence of 0.8 to 2.1 per cent of children among their peptic ulcer patients. A writer reported 5 cases of gastric ulcer among 416 autopsies of children between the ages of 2 and 13, and another writer found an incidence of 0.3 to 1.0 per cent among 10,845 autopsies of children. A total of about 150 cases of peptic ulcer in children is on record. The incidence seems to be on the increase, in the same manner as in adults, although more thorough particularly roentgenological studies may be responsible for this increase. In adults, men are more frequently involved than females and the duodenum more frequently than the stomach; these conditions seem to apply to children as well.

The younger the child the more unspecific the symptoms. Vomiting and cramps dominate the syndrome in preschool children while in older children the syndrome resembles more closely that in adults. Perforative peritonitis may be the first sign. According to two writers most children with gastric ulcer have normal or low gastric acidity, while in duodenal ulcer hyperacidity and hypersecretion are found in 85 per cent.

Hemorrhage, perforation and stenosis are the most frequent complications, and may develop within a shorter period of time than in adults. Treatment is general-

ly the same as in adults but surgical indication should be much stricter and should be limited to severe hemorrhages, stenoses and perforations.

In order to get a clearer picture of the actual incidence of peptic ulcer in children the author sent a questionnaire to all children's departments of Swedish hospitals, a total of 26; only roentgenologically confirmed cases were considered. Answers were received from 25 hospitals. Over a period of five years, 30 cases of peptic ulcer in older children were observed in these hospitals; this figure must be considered as minimum as probably many more cases were not diagnosed or cared for in surgical departments or in hospitals without special pediatric departments, and it indicates that the disease is not as rare as assumed and that it should always be taken into diagnostic consideration. One child was 3, one 6, one 8, two 9, six 10, five 11, four 12, five 13, and five 14 years old. There were 20 boys and 10 girls, with 17 and 7 duodenal ulcers, respectively.

The symptomatology was not considered in the questionnaire, but of the author's own 6 cases paternal heredity was present in 3. Four children showed typical periodicity of the disturbances. All children complained of epigastric pain, some with radiation towards the back. Three of the 5 children with duodenal ulcer complained of typical hunger pain. Only 1 child had vomiting. The questionnaire had shown low acidity in 2, high acidity in 8, and normal acidity in 16 cases. Blood in the stools had been found in 6 children. Thus generally the syndrome resembles that in adults.

Dietary treatment was instituted in all cases. In 1 case in spite of transitory improvement later an acute perforation took place, requiring operation; suture was done and a relapse occurred later. One child showed no definite improvement after two courses of dietary treatment and a Billroth type I operation was carried out successfully. Cure was reported in 21 cases and improvement in 6; 8 children had relapses, but the period of observation is probably too short to permit definite conclusions concerning the frequency of relapses. Generally, the results of dietary treatment seem to be favorable.

Parahemophilia, a Hitherto Unknown Hemorrhagic Disease — STRANSKY, EUGENE AND DAUISLAWAS, DOMICIANA F. — *Acta paediatrica*, 37: 323, 1949.

"While the symptomatology of hemophilia is well known, there are different opinions as to the etiology. All agree however, that hemophilia is characterized by prolonged coagulation time; the clotting time may vary, but it is never normal. On the average it is around 2 hours, sometimes even 7 to 12 hours. Thus a constantly prolonged clotting time is an inherent factor in the etiology of the disease and stressed in the definitions of it."

Recently the writers observed a family the symptomatology of whose disease definitely suggested hemophilia. "The bleeding tendency had been familial, congenital, affecting only male members of the family, and the bleeding had been definitely traumatic and not spontaneous. But the coagulation time was always normal." The writers could rule out all other known forms of hemorrhagic diseases. As the symptoms had been hemophilia-like, while the clotting time was normal, the writers labeled the cases as "parahemophilia," a hemophilia-like disease, but probably different in etiology and different in the cause of bleeding.

"Carlos, S. D., a 2 year old Filipino male child, was admitted on October 14, 1948, on account of uncontrollable bleeding from a wound in the occipital region. On the day before admission, the child had bumped his skull against the edge of a closet. Bleeding was profuse. A physician sutured the wound with two stitches; the bleeding stopped for half an hour and then started again. One-half year before admission a small wound on the right thumb had bled profusely for one week. For one year the child had been suffering from repeated ecchymoses all over the body.

"Upon admission the child was strikingly pale. There was continuous profuse bleeding from the sutured wound. The child was well nourished and well developed; on objective findings there were besides the bleeding some ecchymotic patches at the right buttock and popliteal area, and a small hematoma in the right malleolar region." The blood findings were as follows:

Hemoglobin	3.5 Gm. per 100 cc. blood
Red cell count	2,470,000 per cu. mm. blood
White cell count	7,400 per cu. mm. blood
Platelet count	420,000 per cu. mm. blood
Volume-packed red cells	17.0 per cent
Mean corpuscular volume	68.8 cu. mi.
Mean corpuscular hemoglobin	14.1 mi. mi.
Mean corpuscular hemoglobin concentration	20.5 per cent
Volume index	0.79
Color index	0.49
Saturation index	0.60
Clotting time	5 minutes (venous blood)
Bleeding time	35 seconds
Prothrombin time	31 seconds
Retractility of the clot	completely normal
Tourniquet test	negative
Capillaries of the nail	normal, no tortuosities

	B	E	M	J	St	S	L	Mo
Differential count:	—	2.4	—	—	4.0	53.6	32.8	7.2

There was marked anisocytosis, poikilocytosis, polychromatophilia, microcytosis, hypochromia; no nucleated red cells, post-hemorrhagic acute anemia. Stool examination: Ascaris ova ÷ no other pathological findings.

"At first, topical thrombin was applied on the bleeding wound. The bleeding did not stop, however, and therefore blood transfusion (190 cc.) was administered on the day of admission. As the bleeding did not stop, 250 cc. blood was administered again the next day. After the second transfusion there was some slight oozing of blood, but the hemorrhage was stopped completely. Two more blood examinations were made afterwards. On October 22, the hemoglobin level was 4.2 Gm. per cent; on November 1, 7.4 Gm." On October 22, there were 4 nucleated red cells to 250 white cells; on November 1, there were no nucleated red cells. The child went home much improved and free of hemorrhagic symptoms on November 1.

The oldest brother of the writers' case was observed in the Philippine General Hospital in 1945. "At that time he was suffering from bleeding from the gums owing to a ruptured swelling of a periostitis of a molar. He suffered, like his younger brother, from profuse hemorrhage following the rupture of an occipital boil. Between the ages of 4 and 7 he also suffered from traumatic bleedings and from time to time had recurrent ecchymotic bleedings as well. There had been hemorrhages in the right knee and elbow joint, at which time a clotting time of 16 minutes and 45 seconds for venous blood was reported along with normal platelet count with normal bleeding time and normal retractility of the clot." The writers examined the blood of this boy again during the stay of his younger brother and found:

Hemoglobin	11.15 Gm. per 100 cc. blood
Red cell count	4,430,000 per cu. mm. blood
White cell count	4,400 per cu. mm. blood
Volume-packed red cells	31.0 per cent
Mean corpuscular volume	70.0 cu. mi.
Mean corpuscular hemoglobin	22.4 mi. mi.
Mean corpuscular hemoglobin concentration	32.0 per cent
Volume index	0.80
Color index	0.78
Saturation index	0.94

	B	E	M	J	St	S	L	Mo
Differential count:	—	15.2	—	—	3.2	48.0	27.2	6.4

There were no signs of anemia. The eosinophilia was due to ascariasis.
The coagulation time (venous blood) was seven minutes and retractility of the clot normal.

Table I. Differential Diagnosis of Hemorrhagic Diseases

	Heredity	Sex	Clotting Time	Bleeding Time	Retractility of Clot	Platelet Count	Fibrinogen	Prothrombin	Capillary Fragility	Purpuric Spots	Ecchymoses
1. Hemophilia	yes	males	much prolonged	normal	normal	normal	normal	normal	normal	absent	present
2. Parahemophilia	"	" ?	normal	"	"	"	"	"	"	"	"
3. Willebrand's Syndrome	"	both sexes	"	prolonged	"	"	"	"	increased	"	"
4. Hereditary Thrombasthenia	"	"	"	" ?	poor	"	"	"	normal or increased	present	may be present
5. Thrombopenic Purpura	no	"	"	"	very poor	decreased	"	"	increased	"	may be present
6. Vascular Purpura	"	"	"	normal	normal	normal	"	"	normal or increased	"	mostly absent
7. Hereditary Hemorrhagic Telangiectasis	yes	"	"	"	"	"	"	"	normal	absent	"
8. Afibrinogenia Congenita	"	"	absent	"		"	absent	"	"	"	present
Acquired Fibrinopenia	no		very prolonged				decreased				

"Thus it may be stressed that even in this brother with history and symptoms strongly suggesting hemophilia, the coagulation time turned out to be normal."

The first cousin of the two boys was admitted in 1946 with hemarthrosis, ecchymoses and a history of traumatic bleedings. "There had been no anemia; platelet count normal, clotting time 7'30" (venous blood), bleeding time 1'30", retractility of the clot normal, tourniquet test negative."

From the family tree the heredity pattern ruled out immediately, even without consideration of other hematologic symptoms, thrombasthenia and hereditary thrombopathy.

The writers summarize in a table the symptomatology of the different hemorrhagic diseases with the exception of the hemorrhages due to prothrombinopenia.

Treatment of Erythroblastosis — Molony, Clement J. — *California Medicine*, 72: 89 (February) 1950.

The writer's presentation is concerned with the total experiences in Southern California with substitution transfusion in the treatment of erythroblastosis, as well as with the mistakes that have been made and with suggestions for the safe and proper use of the procedure.

"Table 1 lists the data, which seem to indicate that substitution transfusion has not lowered the mortality rate in Southern California; in fact, it seems to have raised it. However, most of the cases in which substitution was used were severe, whereas most of those handled conservatively were mild.

"In addition, the number of cases of cerebral damage that came to light was most alarming. About 15 per cent of the patients who lived turned out to be abnormal, either athetoid or simply slow in mental development. . . . Most students of the disease feel that the damage takes place in utero and that no procedure will alter the development of this complication. It is interesting that these cases tended to be associated with very high maternal antibody titer."

"Other positive and interesting findings included:

"1. The history of a preceding sibling with erythroblastosis did not carry a particularly bad prognosis."

Table 1.—Mortality Rates from Erythroblastosis in Southern California

	Number of Cases	Deaths	%
Cases in which substitution was used	45	13	29
Children's Hospital	16	4	25
Other hospitals	29	9	31
Cases in which substitution was not used: Children's Hospital	35	5	14
Total Children's Hospital experience	51	9	18

"2. Erythroblastosis occurs most commonly in the second pregnancy.

"3. Prenatal antibody titers had a definite correlation with the severity of the disease. However, the author disagrees with many of the workers in the field who state that a very high maternal titer invariably means a serious case with a high death rate. In 10 cases in this series the titer was 1:256 or more, yet the patients lived and are well, half of them without having had substitution transfusion.

"4. Substitution transfusions definitely cut down the length of hospital stay and the number of subsequent transfusions needed.

"One relatively unpublicized procedure which has been most helpful has been the Coombs test, sometimes known as the developing test or the antiglobulin test. With this procedure used on the baby's cord blood it is possible to determine the presence of sensitized cells and the titer of any free maternal antibody, and thus get an idea of the probable severity of the disease—all before the baby may show any clinical evidence of erythroblastosis. Obviously such information is of value in determining whether or not to use substitution transfusion. . . . Substitution transfusion should not be considered if the Coombs test reaction is weak."

The use of Rh hapten for treatment should be mentioned. This is an extract of Rh-positive blood. "It is lipid in nature and nonantigenic; it is said to specifically inhibit anti-Rh agglutinins and appears to be a hapten. The material was used throughout pregnancy in 1 very severe case and, in this instance, was of no value. The baby, which was born prematurely at seven and one-half months, was hydropic and died a few minutes after birth. . . . Further work along the line of producing a neutralizing serum to be given the mother during pregnancy is certainly indicated.

"Although many errors in technique have been made in use of substitution transfusion, the author feels that this 'growing-up' period is now over and in the future the procedure can be used with relative safety and facility. So that others may not fall into error, the following list of dangers is presented:

"1. In some cases not enough blood was given. For a baby of any size, at least 500 cc. is needed to supplant approximately 90 per cent of the original blood.

"2. Transfusion was too long delayed. It should be done immediately after the Coombs test results are known and the type of blood determined.

"3. Blood was injected into the umbilical vein. In 1 case the umbilical vein ruptured, and in another thrombosis developed in the portal vein. The patients died.

"4. Calcium was injected into the intravenous tubing. One patient died immediately afterward.

"5. Protection of the infant against exposure, before, during and after the substitution, was omitted. Two infants had rectal temperature of 94° on admission to the hospital and 2 others had very low fluid intake for days before death.

"The following plan of procedure eliminates the dangers listed and is relatively simple:

"1. A set of indications should be established. (The author considers these factors as criteria: (1) maternal history in-

dicative of erythroblastosis, (2) high maternal antibody titer, (3) baby born with evident disease or developing the disease in 8 to 12 hours. Every decision is based upon the Coombs test reaction.)

"2. Liaison with the obstetrician should be maintained so that titers are determined and transfusion can be undertaken without delay. In selected cases premature delivery may be indicated. The cord should be left long. It is probably best to clamp the cord early.

"3. Helpful laboratory work on cord blood would be a cell count and smear for nucleated red cells, an icteric index, and a Coombs test.

"4. The substitution should be as soon as possible.

"5. The baby should be kept warm and in an oxygen tent from birth in severe cases.

"6. The blood should be drawn out through the umbilicus, using the Diamond plastic catheter, and the substituted blood should be put in through the saphenous vein via a cutdown at the ankle. Two persons should do the substitution and the rate of injection should be exactly equal to the rate of withdrawal so that there is no chance of overloading the circulatory system. A 1:1,000 heparin solution in small amounts may be used to clean out the umbilical catheter if it becomes plugged.

"7. Rh-negative, type specific blood should be used—at least 500 cc., and more if the maternal history indicates severe difficulty and the condition of the infant is poor.

"8. Calcium is not really necessary. If it is given, it should never be injected into the tubing, but very slowly and directly into the vein.

"9. After transfusion, the infant should be given fluids subcutaneously and kept in an oxygen tent.

"10. Teamwork should be developed at the hospital among physicians called upon to treat erythroblastosis, so that one may be immediately available to assist the resident and to check on details.

"Although substitution transfusion in the treatment of erythroblastosis has given disappointing results in Southern California thus far, technique is improving and ultimately a reduction in mortality rate may be achieved. It is noteworthy that in the last 12 cases (6 quite severe) in which the procedure has been used, the patients have all gotten along well. Material for the Coombs test is now generally available to laboratories, and it is recommended that the test be used to assist in planning a course of action."

Symposium Section

Anticoagulant Therapy

In this section last month attention was called to the indifference manifested by workers on current problems to information that has been laboriously collected and correlated in the past. This was one of three attitudes suggested by Dr. Homer F. Swift of the Rockefeller Hospital in his Kober Lecture. Anyone whose duty it has been to analyze medical literature has had an especially favorable opportunity to observe this to the extent that unpleasant thoughts have had to be suppressed. In recent years, however, the tendency to reexamine collected and correlated information has been increasing and it has paid off in rich dividends. For example, insulin, the sulfonamides and penicillin were the rewards of continuing along trails which were blazed by pioneers who had too little time. Luckily younger, and maybe better trained, generations took advantage of modern facilities to overcome the limitations which made the road too rough for those grown tired, and attained successes far greater than the earlier workers ever hoped could be reached.

Another example with which we are here concerned occurred in 1916. McLean, a second year medical student working in the laboratory of the eminent physiologist Howell of Johns Hopkins University, discovered a substance which initiated a therapeutic procedure now prolonging human life but he certainly never dreamed of what it was eventually to become. In fact he was working in the opposite direction. At the time interest was high in discovering substances that would accelerate the clotting of blood and young McLean was attempting to purify thromboplastic phosphatides from various tissues when he obtained a substance that not only failed to hasten coagulation but actually inhibited it. Professor Howell's interest in the new substance was immediately aroused, and during the next several years he established its identity as a polysaccharide and described methods for its extraction and purification. Because of its comparatively high concentration in the liver it was named *heparin*. Howell noted its lack of toxicity and as early as 1917 suggested that it might be useful "in the therapeutic treatment of disorders of coagulation." It was not until 1935 that purified heparin became available in sufficient amount for trial in human subjects and the first clinical studies appeared in 1937 when Murray, Jaques, Perrett and Best in America and Crafoord (now so prominent in cardiac surgery) in Sweden reported their experiences. The first group used it in thrombosis of veins following injury and Crafoord tried it as a postoperative measure to prevent thrombosis. This was 20 years after Howell's suggestion.

* * *

For several years heparin was the only anticoagulant in use. Consequently, ample opportunity was afforded to learn its advantages and its disadvantages. It was soon realized that it was desirable to develop other substances because heparin was usually given intravenously and was quite expensive. Then came another interesting story of the discovery of the second anticoagulant *dicoumarol*. It seems that as long as 30 years ago veterinarians and cattle raisers had observed that cattle were occasionally affected by a hemorrhagic disease in which the bleeding often proved fatal. It usually occurred suddenly for no apparent reason. So two veterinarians, Schofield and Roderick, at the North Dakota Agricultural Experiment Station, started an investigation which finally resulted in the observation that this mysterious disease was caused by the cattle eating improperly cured clover hay or spoiled sweet clover silage. So the condition became known as "sweet clover disease of cattle"; it continued to occur in spite of efforts to prevent the spoiling of the sweet clover hay and in 1934 Professor Karl

Paul Link and his associates, of the Wisconsin Agricultural Experiment Station at the University of Wisconsin, began a carefully conducted and brilliantly conceived series of studies which seven years later culminated in the isolation and synthesis of the active hemorrhagic agent in the spoiled clover which was causing the disease in cattle. The possibility of using this agent as an anticoagulant was immediately appreciated and the efforts of those interested in this form of therapy were soon concentrated on determining its pharmacologic and therapeutic properties.

The substance which was isolated is a tasteless, odorless, white crystalline powder and was, at first, called *dicoumarin*. This was suggested by its chemical structure 3,3′-methylenebis (4-hydroxycoumarin) and paradoxically, as has been frequently noted but not widely emphasized, its structure is very similar to vitamin K which is used to antagonize its effect. It is now known as *dicumarol* and is available in capsules which conveniently may be administered by mouth.

* * *

So far heparin can be given three different ways but all of them are by needle. A recent breakdown of these methods by Reich and Eisenmenger briefly describes them. The first method provides for a continuous drip at the rate of precisely 30 drops a minute of a 10 cc. vial of heparin containing 10 mg. added to 500 cc. of saline solution. A coagulation time is done every four hours by the Lee-White method and the object, of course, is to prolong the coagulation time three times normal. Usually this can be maintained satisfactorily provided nursing care is sufficient to control the drip so that variations in the flow will not cause changes in the coagulation time.

The second method is to inject the heparin (50 to 100 mg.) into the vein every four to six hours without diluting it. This has the disadvantage of frequent injections, but Jorpes of the Caroline Institute in Stockholm, whose experience has been extensive in Sweden, contends that these injections need not be controlled by coagulation determinations except under special conditions, such as elderly persons with impaired renal function. He further says, by this method "heparin treatment can be given at any hospital, even the smallest ones, and if necessary at the home of the patient. The bleeding tendency is not very pronounced." It is clear that investigators and clinicians in this country do not wholly agree with this opinion.

The third method of giving heparin as was suggested by Loewe is to inject 200 to 400 mg. in the deep subcutaneous tissues at 48 hour intervals. The heparin is given in Pitkin's menstruum.

Regardless of how heparin is given, the consensus is that the coagulation time should be checked sufficiently often to safeguard against hemorrhage which seems a danger which must be borne in mind whenever this prompt-acting anticoagulant is used. Intravenous administration seems to be the only effective way to use it. Allen and his associates, of the Division of Medicine of the Mayo Clinic, who have been leaders in anticoagulant therapy since it began, write that "heparin . . . . has the advantage of quick action (within a few minutes after intravenous injection) and quick cessation of action (about three hours after injection)," and that "it can be satisfactorily administered without 'laboratory control.'" We do not gain the impression from their writings that they believe that the use of the drug can be as indiscriminate as the opinion of Jorpes conveys. There seems to be general agreement that the main disadvantages of heparin are the relative great cost and the need of parenteral administration.

* * *

Dicumarol is administered orally. Clinical studies, particularly those at the Mayo Clinic, have established that thrombosis seldom occurs if prothrombin activity is less than 30 per cent of normal and that hemorrhage seldom occurs if prothrombin activity is greater than 10 per cent of normal. The therapeutic objective of maintaining the prothrombin activity within these limits can be achieved only by variation of the dose of dicumarol to fit the response of the individual patient. Ordinarily 300 mg. is a safe initial dose. Thereafter, it is imperative to adjust the dose according to the prothrombin activity determined once each day. If the prothrombin activity is greater than 20 per cent, 100 to

200 mg. is given. If it is less than 20 per cent none is given. However, some attention must also be paid to the rate of change of prothrombin. If, for example, it is falling rapidly but has not yet reached 20 per cent, it would be injudicious to give more. Furthermore, if the patient is unusually sensitive or unusually resistant, the daily dose may need to be less than 100 or more than 200 mg. Indeed it is impossible to give any hard and fast rules for administering dicumarol; the proper dosage schedule must be determined for each patient by a system of intelligent trial and error.

Since the effectiveness and safety of dicumarol treatment are wholly dependent upon reliable prothrombin estimations, it is most unfortunate that the determination and interpretation of prothrombin times differ widely from clinic to clinic. The one stage method of Quick, or some modification thereof, has been most extensively used. In this technic oxalated plasma is allowed to react with optimal concentrations of thromboplastin and calcium and the time needed for clot formation is measured. Because preparations of thromboplastin may differ in potency, it is essential to test each new preparation on several normal plasmas. Moreover, the relation between prothrombin time and prothrombin concentration is far from linear. A curve relating the two variables should be determined in each laboratory for each batch of thromboplastin by measurement of the prothrombin times for various prothrombin concentrations obtained by dilution of normal plasmas with saline solution or with prothrombin free plasma. From such a curve unknown plasmas can be read and reported in terms of percentage of normal. This mode of expressing the results tends to eliminate differences due to variations in thromboplastin and facilitates accurate regulation of dicumarol dosage.

Far worse than reporting results simply as prothrombin time is the completely misleading, but apparently very widespread, practice of calculating "percentage of prothrombin" by division of the prothrombin time for normal plasma by the prothrombin time for the unknown sample, the result being multiplied by 100. This mode of calculation is based on the erroneous assumption that if the prothrombin concentration is halved, the prothrombin time is doubled. It grossly overestimates prothrombin activity, and when used as a guide in attempts to maintain prothrombin between 10 and 30 per cent of normal, may lead to serious overdosage.

Link insists that the Quick method is too insensitive to give reliable results and is vigorously in support of the use of plasma diluted 1:8 with saline solution. Although it is true that Quick's method may fail to detect small decreases in prothrombin activity, these are not usually of clinical significance. In the range below 30 per cent of normal, most investigators have found the Quick procedure entirely adequate, whereas in the same range the end point with Link's 12.5 per cent plasma is difficult to determine.

In the "two stage" method of Smith and his co-workers, the prothrombin is completely converted to thrombin after the removal of fibrinogen. The time needed for formation of a clot in a specially prepared solution of fibrinogen is then measured. Although this method eliminates variability due to differences in the rate of thrombin formation, and, therefore, provides a more exact estimate of the actual concentration of prothrombin, the technic required is too intricate and takes too much time for general use. Furthermore, alterations in rate of thrombin formation may actually be caused by dicumarol and may help to determine its clinical effect. In a detailed comparison of prothrombin methods used for controlling dicumarol therapy, Olwin found the least day-to-day variation in prothrombin activity by the two stage method, but he also stated that "the one stage method is of value in estimating the summation of the various clotting factors."

The so-called "bedside method" for prothrombin determination is much too unreliable for use in control of dicumarol administration and at present dicumarol cannot be safely employed unless the facilities of a properly equipped clinical laboratory are available.

* * *

It is probably widely appreciated that the sole danger associated with the use of anticoagulants is hemorrhage. In a series of 1,983 postoperative cases, the Allen group encountered minor hemorrhage

(epistaxis, hematuria and localized ecchymosis) in 3.4 per cent of the cases and serious bleeding (from operation wounds or the gastrointestinal tract) in 1.8 per cent. This would seem to be a small risk but it should be remembered that these figures come from an experienced group with limitless facilities.

From experience obtained from the earliest use of anticoagulants, they have learned many of the contraindications to the use of this form of therapy. Among the conditions in which anticoagulants are to be used cautiously or not at all are: (1) ascorbic acid and vitamin K deficiencies and hepatic diseases, in which anticoagulants are not needed and the use of them may magnify the tendency to bleed, with disastrous results; (2) renal insufficiency, in which the dicumarol effect would be enhanced and prolonged by abnormal accumulation; (3) any blood dyscrasias which impair the normal mechanism which controls and prevents bleeding; (4) recent surgical operations on the brain or spinal cord in which even slight hemorrhage may be disastrous; (5) ulcerative lesions or open wounds in which the tendency toward bleeding is very great. These should suggest other conditions in which caution should be practiced.

It is admitted by experienced groups that when anticoagulants are used by experts under the most favorable and convenient surroundings hemorrhages may occur. A number of reports have been published to substantiate this. For the control of the more serious hemorrhages synthetic vitamin K (menadione bisulfite) should be administered intravenously in amounts of 60 mg., and a transfusion of fresh blood should be used to restore the blood which has been lost. The intravenous vitamin K can be repeated at two hour intervals, once or twice as needed. The anticoagulant being used at the time should, of course, be discontinued.

* * *

So it seems that at the present time interest is high in anticoagulant therapy. So far its use in subacute bacterial endocarditis has been eliminated, in several other conditions its value is becoming questionable and in others the benefits which it is hoped will be derived from it are not fully determined. We have reviewed all the articles which have come from authoritative centers and many from individuals who have been encouraged to try it independently. From these we think that it is not possible at present to make a fair appraisal. Even the outstanding authorities are reluctant to reach preliminary conclusions until present studies are completed and confirmatory investigations are undertaken to check definite discrepancies. Nevertheless, anticoagulants have been beneficial in many conditions for which no satisfactory treatment previously existed. If clinical evidence continues to be reported which is as favorable as some of it has been, enthusiasm is going to be fully justified.

We have previously indicated that Allen and his associates at the Mayo Clinic have diligently worked with anticoagulants since they were first suggested, so their opinion does offer a conservative evaluation and represents present impressions. In a recent report they say, "in general the use of anticoagulants constitutes the greatest contribution to the successful treatment and prevention of intravascular thrombosis and embolism." But to illustrate the need for further contemplation and more definite opinion this same group tells us that "in considering venous thrombosis and pulmonary embolism there is one most desirable goal"—absolute prevention. "This," they say, "has not been achieved." In connection with it they relate that 832 patients who had undergone abdominal hysterectomy were treated with dicumarol in order to save 6 lives and to prevent venous thrombosis and nonfatal pulmonary embolism in 30 instances. "The returns," they say, "might be considered small." Their numerical results are more impressive in cases of venous thrombosis and embolism; yet it was necessary in the aggregate to treat 681 patients in order to save 79 lives and to prevent further venous thrombosis and embolism in 220 instances. "We do not belittle these results," they say, "we only emphasize our inability to detect the predisposition to venous thrombosis before it occurs." They consider that if it were possible to designate the patients who would have venous thrombosis before they had it, treatment with anticoagulants would be even more productive.

"There has been a good deal of study . . . . but the hard core of the problem remains."

This is, indeed, an unusual and refreshing interpretation of statistics which clearly illustrates the conservatism and conscientiousness of a competent group. It certainly inspires confidence and merits the gratitude of those who feel the need of guidance. In no way could the present status of the anticoagulants be better expressed.

* * *

Heparin and dicumarol have been used singly and in combination in all types of thromboembolic disease and have been effective both in alleviating most of them and in prolonging human life. Neither of them can be considered ideal. Hope has been expressed that an anticoagulant may eventually be found that will combine the best qualities of each. Meanwhile there is every reason why they should be relied on in the management of conditions in which anticoagulant therapy is indicated. They are not without danger, however, and when they are used vigilance in utilizing measures of control cannot be disregarded. Hemorrhage is still their greatest danger but most fatal cases from this cause have usually been the result of neglect of essential precautionary controls.

The following recent articles are suggested as collateral reading and to each of them is appended extensive bibliographies:

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Riggs, D. S.: Medical Progress: Anticoagulants (Part I), *New England J. Med.*, **242:**179 (February 2) 1950; (Part II), **242:**216 (February 9) 1950.

de Takats, G.: Anticoagulant Therapy in Surgery, *J. A. M. A.*, **142:**527 (February 25) 1950.

Dermatitis Accentuated by Gauze

A 27 year old librarian was receiving treatment on account of a typical atopic dermatitis of long duration. "Her forehead, neck, shoulders, antecubital fossae, wrists and arms presented patches of dermatitis in various stages of development. She also suffered from seasonal hay fever. Two other members of her family presented similar difficulty at various times."

It is the writer's custom to try out a number of test ointments at various affected areas before he decides which one is to be relied on. "The test ointments were covered with gauze and then secured with a loosely applied roller bandage.

"Within a short time the patient complained of burning at all the test areas. The applications were of course removed at once, with the use of warm mineral oil. Except for the fact that the dermatitis seemed more acute, nothing of note was recorded.

"To permit the subsidence of the dermatitis accentuated by the test ointments, the patient was instructed to return in three days, having applied nothing to her skin and having refrained from washing during the interval.

"On her return three areas of dermatitis were selected and bandaged with several layers of sterile gauze so that on each area there was the product of a different manufacturer. Within 10 minutes burning was experienced at all the areas, and on the removal of the gauze dressings the observation of a noticeable increase in redness testified to the veracity of the patient's complaint.

"Similar gauze patch tests were now applied to normal-appearing cutaneous surfaces and left in place for 48 hours. No reaction was noted at the end of this period at these sites."—Lester Hollander, *Archives of Dermatology and Syphilology*, 61: 118 (January) 1950.

International Medical Digest

A Monthly Abstract Journal of Current Literature

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Fatal Iron Poisoning

In two recent issues of the *British Medical Journal* there appeared reports of fatal poisoning by iron preparations which are commonly used. The first was a case of a child who died after swallowing a number of pills containing iron, manganese and copper. Other similar cases have been described, and no doubt there is a danger that young children might be attracted by the appearance of the sugar-coated tablets and swallow them. The second is a report of a fatal case of poisoning by a different preparation of iron. This time the deceased was an adult woman who had taken ½ ounce (15. Gm.) of iron and ammonium citrate; she was pregnant and apparently took the drug to procure abortion. The official maximum dose is 40 grains (2.6 Gm.). There was distinct evidence of corrosive action caused by the ferrous sulfate, but no mention is made of the condition of the stomach. The death was ascribed to hepatitis due to iron poisoning. The citrate in iron and ammonium citrate serves as a buffer, so that this preparation occupies an intermediate position between ferrous sulfate and ferrous carbonate. The risk of poisoning is less than with the sulfate, but the absorption of iron, and therefore the efficiency, is also less. Any danger that exists depends on susceptibility and dose. Preparations of iron are not scheduled poisons, but the recent fatalities will no doubt put practitioners on their guard, especially in prescribing iron for children.

The Adaptation Syndrome

With the turn of the half century has come a most extraordinary conception of just what stimulates the production of hormones in the human body which may revolutionize our entire approach to diseases. This radical departure is truly what might be expected to come during this new era when everyone is jittery over what may happen next. It comes from Professor Hans Selye, Director of the Institute of Experimental Medicine and Surgery of the University of Montreal, Canada. Most of his earlier papers have appeared in British or Canadian journals of prominence but it has taken some time for his amazing theories to become widely appreciated. Moreover, they have been rather difficult to follow and understand. In his most recent paper in the *British Medical Journal* he discusses further work on the pathogenesis of "diseases of adaptation."

As a result of experimental work on animals, Selye has suggested that following exposure to stress—a term used to include such diverse conditions as emotional tension, infections and intoxications—the body responds by increased production of hormones from the adrenal cortex. These hormones help to raise the general resistance of the body to the stress to which it is subjected. Selye maintains that this adaptive mechanism may itself become deranged, and he has produced in animals a variety of conditions which are perhaps the experimental counterparts of rheumatoid arthritis, rheumatic fever, nephrosclerosis, hypertension and periarteritis nodosa. The adrenal cortical hormones may be broadly divided into two main groups— the gluco-corticoids (such as corticosterone and cortisone) and the mineralo-corticoids (such as desoxycorticosterone or DCA). The two groups differ in their effect on the organism. In experimental animals Selye found that corticosterone increased, whereas desoxycorticosterone diminished, the resistance to traumatic shock. Overdosage with desoxycorticosterone itself may induce the conditions mentioned above, especially if the animal has previously undergone unilateral nephrectomy and is given a diet with high salt content. It is

suggested, therefore, that stress causes the adrenals to liberate cortical hormones, and if there is disproportionate overproduction of the mineralo-corticoids the diseases of adaptation may appear.

Two main objections have been raised to this experimental work. First, contrary to widespread belief, there is little evidence that desoxycorticosterone is a naturally occurring substance or that it is secreted by the adrenal cortex. It has only once been isolated from the suprarenal glands, and this may well have been an artefact produced in the laboratory. Secondly, since desoxycorticosterone does not occur naturally, the reactions it provokes may be the allergic responses of the body to a foreign substance. Professor Selye now reports some observations which go far toward dispelling these objections. A naturally occurring mineralo-corticoid, 11-desoxycortisone, has been injected into rats which have been "conditioned" by a unilateral nephrectomy and the administration of excess sodium. The lesions produced (nephrosclerosis, hypertension, periarteritis nodosa, and granulomatous nodules in the heart) are similar to those seen after overdosage with desoxycorticosterone.

It remains to be seen how the results of these experiments on rats with one kidney removed, given much salt and injected with large doses of mineralo-corticoid hormone can be compared with diseases in man. Selye has shown in animals that a gluco-corticoid (cortisone) will inhibit the development of adaptation diseases which can be induced by desoxycorticosterone. Similarly it has been shown in man that cortisone will relieve the symptoms not only of the rheumatoid arthritis but also of rheumatic fever, chorea, gout, ulcerative colitis, lupus erythematosus diffusa, scleroderma and asthma. It is tempting in the absence of any known cause for these conditions to suppose that they are the products of disordered adaptation, but as yet there is little evidence for such an assumption. It is unlikely that treatment with cortisone is merely replacement therapy.

In any event further work from Professor Selye's laboratory will be watched with interest.

Dermatitis from Nylon Hair Nets

Recently, the writer has seen several women presenting an extremely severe acute dermatitis of the face, ears, neck and arms. "Historically the dermatitis was of acute onset, and clinically it resembled an acute dermatitis seen in sensitivity to hair dye. The history elicited the information that the dermatitis first appeared on the forehead and the ears. It was finally determined that these patients were allergic to brown nylon hair nets which they purchased at different variety stores.

"These nylon hair nets were used for various purposes, such as keeping the hair in place after a wave set or keeping the hair from being mussed up while the patient was sleeping. Strongly positive reactions to patch tests were obtained. The patients were tested with items such as various dyes and nail lacquers, and no cross sensitivities were demonstrated. Patch tests were made on one woman with a nylon hair net which had been washed several times, and a strongly positive reaction was obtained. None of these women was found to be allergic to nylon stockings."—C. Russell Anderson, *Archives of Dermatology and Syphilology*, 61: 111 (January) 1950.